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RESEARCH IN ORAL SURGERY; AN EDITORIAL

F. A. HENNY

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The development of additional, well-conceived research programs in oral surgery is urgently needed. The recent allocation of funds by Congress for adequate research in dentistry highlights the shortcomings of our present facilities and the need for additional personnel to work in this field. Some research should necessarily be basic in nature whereas other work might well have immediate clinical application. In either event, sufficient funds are available for deserving projects and should be utilized in working toward the solution of the many pressing problems that we face.

The correlation between the heavy use of alcohol and tobacco in development of cancer of the mouth which oral surgeons have noted clinically certainly should be corroborated in the laboratory. Such research could easily provide valuable clues to nutritional and chemical states that may be extremely important in the generation of malignant disease. The effect of condylar fractures on growth and development of the mandible is another important project that deserves early attention. Further study of the uses of preserved bone in surgery of the jaws, investigation of the many varied problems of cleft lip and palate, the development of more efficient tranquilizing agents and of agents that would completely control transient bacteremias are but a few examples of the many problems that require early study.

There has been little interest in basic research among oral surgeons in the past. The time has now arrived, however, when a definite program must be evolved if we are to assume our proper responsibilities and occupy a position of justified respect in the future. Such a program should be sponsored, developed and supported by the American Society of Oral Surgeons in cooperation and consultation with the American Dental Association and the National Institute of Dental Research. It must be guided by men who are sufficiently prepared and dedicated to insure its steady growth and development so that in the future we can take pride in having done our part in making the world a better place in which to live. — Fred A. Henny.

THROMBOCYTOPOIESIS IN MAN

JOHN W. REBUCK, Ph.D*., AND RAYMOND W. MONTO, M.D.**

Introduction

The orderly delivery of platelets to the blood is dependent upon the integrity and normal functioning of the megakaryocytic series of cells[1,2] in man.* Normally the bulk of the megakaryocytes are found in the hematopoietic bone marrow. Examination of tissues of cases of "sudden death" by Smith and Butcher[3] revealed that megakaryocytes were located both intra—and extravascularly in bone marrow, spleen and lymph nodes. In the lung, liver, kidney, heart, adrenal, pituitary, cerebrum, cerebellum, pancreas, striated muscles and wall of the aorta the megakaryocytes were intravascular only. In the lungs about three fourths and in the spleen about half of the megakaryocytes were "naked nuclei" without cytoplasm. Although "naked nuclei" were not uncommon in kidney, liver or heart, adult megakaryocytes were unusually so situated. Howell[4] found extensive platelet formation from megakaryocytes in the pulmonary vessels of the dog.

The youngest member of the megakaryocytic series is termed the megakaryoblast,[5] which forms the promegakaryocyte,[5] which in turn forms the megakaryocyte[5] or platelet-forming cell. Ordinarily the megakaryoblast is derived from the myeloblast (hemocytoblast)[6,7,8,9] or from the reticulum cell (mesenchymal cell).[6,8,9,10,11]

Megakaryoblast (Fig. 1-4)

As observed in dry-fixed smears or imprints stained with Romanowsky methods (Wright, May-Grunwald Giemsa) this cell measures 15 to 50 mu which is larger than the myeloblast which it somewhat resembles. The nucleus is round, oval, reniform or indented, and centrally or eccentrically situated. This cell is rarely multinucleated. The nuclear membrane is thin. The chromatin pattern presents small chromatin particles arranged in a fine, sieve-like or regularly stippled pattern which stains somewhat more darkly than the myeloblast pattern. The parachromatin appears as abundant and distinct pink (not blue) granules in between the chromatin meshwork. Nucleoli may be 0 to 10 in number, are pale blue and well circumscribed when present.

The nuclear:cytoplasmic ratio favors the nucleus. The narrow band of cytoplasm is of varying shades of blue, usually zoned in lighter areas near the nucleus and darker more peripherally. In the area of diminished density (Fig. 4), as the megakaryoblast enlarges, a few azurophil granules first make their appearance. These cells do not produce platelets. Viewed with the phase microscope[12] numerous mitochondria occupied the perinuclear zone, the remainder of the cytoplasm was hyaline.

Promegakaryocyte (Fig. 5-7)

Under similar conditions as described for the megakaryoblast this cell measures from 20 to 80 mu and is thus larger than the megakaryoblast. The nucleus, too, is

*All workers cited in the bibliography subsequent to 1906, with the exception of Levy, adhere to this concept. All descriptions and references, unless otherwise stated, concern conditions in man.

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larger than that of its predecessor. The nucleus may be oval but polylobulation begins at this stage. (Fig. 6, 7) The nuclear membrane is still thin but the chromatin pattern stains more heavily than in the megakaryoblast. The regular, distinct network of chromatin remains but the chromatin threads are coarser and may show areas of clumping. The parachromatin shows as smaller pink areas between chromatin strands where they are not clumped. Nucleoli are usually less numerous than in the megakaryoblast but may still be very numerous as in fig. 6. During this stage, growth of cytoplasm proceeds and the nuclear:cytoplasmic ratio is reversed in favor of the latter. The "functional area" of granulopoiesis[13] grows rapidly with the cytoplasm until the entire cell body is filled with azurophilic granulation except for a narrow peripheral transparent blue border. The cytoplasmic background is blue in color but becomes paler blue as maturation approaches. Budding of small and large lobules from the convexity of the nucleus (Fig. 11) may occur. The heavily granulated larger promegakaryocytes have been termed *"Intermediate forms"* by Dameshek and Miller.[10]

An unusual, but normally occurring, variant of this stage possessing a relatively small, distinctly lobulated nucleus imbedded in deeply basophilic cytoplasm almost devoid of granules has been described by the latter authors[10] as *"lymphoid megakaryocyte."* (Their Fig. 6, 7)

Platelet formation may or may not be present at the periphery of the intermediate forms, when viewed with the phase microscope[14] agglutination of cytoplasmic granules formed units resembling granular platelets at the periphery of the cell.

Megakaryocyte (Fig. 8-10)

The megakaryocyte is the largest member of this series and measures from 30 to 160 u. The nucleus is large, polymorphous and complicated in outline. The chromatin strands are so thickened that they form heavy, dark-staining clumped masses with either a few small distinct areas of parachromatin or no parachromatin visible. The nuclear membrane is thick and nucleoli are not visible. The abundant cytoplasm is pale blue to pink in color. The full component of azurophilic granulation extends to the periphery of the cell (active form of Frey[15] and Schwarz[16]) where the granules gradually form groups surrounded by clear areas of cytoplasm. (Fig. 9) The cell body itself begins to show intracytoplasmic dissolution about granular groups. Pseudopodial processes frequently contain platelet-like aggregates of azurophil granules surrounded by clear areas of cytoplasm. For characteristics of the corresponding elements as observed in tissue sections the reader is referred to the excellent illustrations of Downey.[17] For comparison of the other cells described herein as observed in tissue sections please see our earlier report.[18]

Recently Schwarz[16] has deservedly directed attention to a normal variant of the megakaryocyte, the *reserve megakaryocyte* of Frey[15] and Downey.[7] Although similar in granular content to the active form, the reserve or resting cell is spheroid in outline and surrounded by a continuous hyaline envelope itself devoid of any structure or granulation. (cf. Schwarz,[16] Fig. 1-3)

Platelet Formation

Although the intermediate forms are capable of some platelet formation, the active form of the adult megakaryocyte furnishes most of the platelets to the blood. Two forms of platelet production are now recognized, the first or pseudopodial process is

best outlined by its discoverer.[2] "All of the blood platelets are detached portions or fragments of the cytoplasm of the megakaryocytes, which are in such relation to the blood channels in the marrow that detached portions of their cytoplasm are quickly carried by the blood current into the circulation. The breaking up of the cytoplasm into the platelets occurs only in cells which have reached a certain stage of growth and development, and is probably rapidly completed when once begun. It takes place in various ways but usually by the pinching off of small rounded projections or pseudopods from the cell body or from larger pseudopods, or by the segmentation of slender pseudopods, or by pinching off of longer or shorter pseudopods which may or may not undergo segmentation later. All, or most of the cytoplasm of the giant cell is given off to the blood stream and the nucleus degenerates. The more or less naked nucleus if often carried by the blood stream to the lungs where it lodges in the capillaries. Before the separation of a platelet takes place, the red to purple staining granules, in the portion of the cytoplasm which is to form the platelet, are separated from the rest by a zone of hyaline cytoplasm and arranged in a more or less sharply outlined, rounded, or oval mass. The line of cleavage is through this zone of hyaline cytoplasm and this sharply outlined mass of granules becomes the central granular mass of the blood platelet which has been regarded by some observers as a nucleus."

Although continuous observation of this process has not as yet been observed, Wright himself[2] noted in supravital preparations: "In this connection I may state that I have seen a few megakaryocytes change their form very markedly, sending out the withdrawing pseudopods, such as are seen in the sections. This seems to show that the presence of pseudopods and protoplasmic prolongations of megakaryocytes in blood vessels, as I have seen in the sections, is not a passive act, due to local conditions of pressure in the tissue, but is a manifestation of vital activity."

Under the phase microscope Bessis[12] found sperm-like cytoplasmic tongues at the cytoplasmic periphery, the tongues themselves were surmounted by long filamentous projections. (His Fig. 79, 80, 82) In unstained preparations under the dark-field, Saltzman[19] observed that amid all the bone marrow cells, fibrin accumulation occurred only about the megakaryocytes and platelets.

A second mode of platelet formation is one in which the platelets are set free by simultaneous disintegration of large portions of the entire cytoplasm. (Fig. 10) Sabin's supravital studies supported disintegration as a regular process of platelet formation, a process seriously entertained by Schwarz.[21] Recently Pisciotta, Stefanini and Dameshek,[14] utilizing the phase microscope for their studies, described fragmentation of the cell into platelet units by aggregation of the granules toward the periphery of the heavily granulated adult megakaryocytes. "At certain points on the surface, the cell membrane appeared ruptured with an outpouring of numerous granular aggregates or platelets." (Fig. 2, 3, 23) Downey and Nordland[7] observed platelet formation by multinucleated megakaryocytes which possessed small dark nuclei; a similar cell is shown in our fig. 12.

Degenerating Megakaryocytes

Having performed their platelet-producing functions, degeneration is the ultimate fate of the megakaryocytes. Limarzi and Schleicher[22] found 28% degenerating forms

in normal marrow, Japa[23] 36%. The latter author found signs of degeneration beginning at the 8-nuclei stage. The chromatin pattern is coarsened to the stage of pyknosis, pseudohyperlobulation or conversely lobular massing may ensue. The cytoplasm is usually lost to a deeply basophilic rim about the structureless nuclear mass; in the last stage only the naked nuclear remnants are seen. The degenerating megakaryocytes attract granular leukocytes,[24] a condition which may be mistaken for a phagocytic function on the part of the megakaryocyte.[25]

Cellular Division

The megakaryoblasts and promegakaryocytes undergo a type of cellular division in which the nuclei divide by mitosis (fig. 13) but cytoplasmic division is customarily lacking.[4,13,23,26] In addition amitotic forms have been described.[6,27] Schwarz[13] believed that mitoses ceased when the megakaryocyte contained its full complement of granules.[4] The resultant megakaryocytes may be polymorphonuclear and multinuclear cells.[10,26,28] Dameshek and Miller[10] and Epstein[28] believed that the polymorphonuclear forms predominated in normal marrows over the uncommon multinucleated megakaryocytes. (Fig. 14) Japa[23] presented experimental evidence for his concept that all megakaryocytes beyond the early megakaryoblast (1 nucleus) stage are in reality multinucleated. He described megakaryocytes with 2, 4, 8, 16 and 32 nuclei respectively. Instead of describing the process as pluripolar[21] or multipolar mitosis as in common usage he observed that each of the component nuclei formed a bipolar spindle synchronously. Most authors follow the broader views of Dameshek and Miller[10] and Epstein.[28]

The Polykaryocytes

When in 1890, Howell[29] differentiated the polymorphonuclear "megakaryocyte" from the other marrow giant cells, he designated the remaining multinucleated giant cells of the marrow as "polykaryocytes." Di Guglielmo[30] expressed the view that platelet-forming polykaryocytes arose from the fusion of primitive mononuclear cells. As we have seen above (Fig. 14) multinucleated megakaryocytes, although uncommon, may be found in normal marrows. Rather than arising by fusion of mononuclears Japa[23] has presented the alternative and more attractive explanation of their presence, that is the occurrence of nuclear division without cytoplasmic division and without subsequent fusion of the daughter nuclei. Previously we[18] have described, depicted and differentiated, both in tissue sections and marrow aspirates, the normal nonmegakaryocytic multinucleated giant cells of the marrow: osteoclasts, multinucleated plasma cells, and the rare multinucleated erythroblasts. Our fig. 15 again depicts an osteoclast from a marrow aspirate because it is this cell that is most frequently confused with the platelet-forming megakaryocyte and indeed with metastatic carcinoma. The many round or oval, monotonously patterned nuclei, all of a kind, resemble histiocytic or reticulum cell nuclei. One to three deeply basophilic nucleoli are invariably present amid a nuclear pattern of angular distinct chromatin particles irregularly distributed throughout the nucleus. The abundant cytoplasm is a mixture of blue and colorless components. Occasionally the cytoplasm contains small fine numerous or sparse angular large purple inclusions (bone salts).

Leukemic Megakaryocytes

In megakaryocytic leukemia it is possible to observe the bizarre megakaryocytic forms resulting from the leukemic process.[18,31] In figs. 16 and 17 we have reproduced

two luekemic megakaryocytes as seen in tissue sections from a previous report.[18] One can compare their structure with both the definitive megakaryocytes and the Reed-Sternberg cells of Hodgkin's disease. Their nuclei may undergo extreme hyperlobulation, with the formation of massive albeit vesicular nuclei, two or three giant lobes may contain large basophilic nucleoli more prominent than in the definitive megakaryocytic series, but never as large as in Reed-Sternberg cells. (cf. Fig. 18, 19) Recently Schwarz[16] has described abnormal, giant nucleolated megakaryocytes in chronic granulocytic leukemia terminating in a myeloblastic crisis. (cf. his Case 2)

Differentiation of Megakaryocytes from Reed-Sternberg Cells

In sectioned material, differentiation of these two series may pose a difficult problem. In aspirate material however (Fig. 18, 19) the two cell lines show marked nuclear disparity. The Reed-Sternberg cell has increasing giant, bizarre nuclear polylobulation which is characterized by retention of the fine reticular chromatin network with its chromatin-parachromatin distinction. The nucleoli which may reach diameters up to 7 mu are a deep blue color. The cytoplasm may be scant or abundant, is composed of blue and colorless components and is poor or lacking in azurophil granules. If aspirate material is not available for differentiation, Fisher and Hazard[22] have reported that the cytoplasm of the megakaryocyte is strongly positive for the periodic acid-Schiff method in contrast to the Reed-Sternberg cell in sectioned material.

Phagocytic Functions of Megakaryocytes

This subject has long been one of contention. Frank[23] described megakaryocytic erythrophagocytosis as well as phagocytosis of granular leukocytes. Downey, Palmer and Powell[6] and Schwarz[24] similarly described phagocytosis of granular leukocytes. Kabelitz[35] has emphasized that the younger megakaryocytes are especially phagocytic for leukocytes and other cells. Saltzman[25] in contrast has observed in supravital preparations migration of granular leukocytes to the megakaryocytes and occasional destruction of degenerating megakaryocytic forms by the leukocytes.

Time and Spatial Relationships of Megakaryocytes

Characteristically in cases of idiopathic thrombocytopenic purpura, thrombocytopoiesis on the part of the megakaryocytes comes to a standstill. Subsequent to splenectomy, the minimum time that elapsed until resumption of platelet formation by the adult megakaryocytes affords an important clue as to the time needed for the performance of this phase of thrombocytopoiesis. Dameshek and Miller[19] reported well-defined platelet production at the edges of the megakaryocytes within 24 hours. Valentine[35] depicted massive platelet production by mature megakaryocytes within 48 hours.

Downey and his associates[6] and Schwarz[16] have commented on the inferiority of extramedullary megakaryocytic platelet-production compared to intramedullary production.

Histochemical Studies of Megakaryocytes and a Comparison of Comparable Histochemical Studies in Platelets

Our table I outlines the histochemistry of the megakaryocytes and platelets as reported in the literature. All the tests listed were performed on human material except

those noted for RNA.[44] which were performed on the marrows of rhesus monkeys and guinea pigs. The importance of true polysaccharides in the metabolism of the megakaryocytes is attested to by the first 11 tests listed. Furthermore the phosphatases underline not only carbohydrate metabolism but are importanly related to nucleoprotein metabolism[43] as well. The presence of a positive plasmal reaction[39] indicates the presence of glyceryl-phosphoryl-ethanolamine and possible related compounds. The 13th to 17th tests are related to mitochondrial activity. Bloom and Wislocki[40] in commenting on the sudanophobia of human platelets suggested that the platelet mitochondria had become swollen and had lost some of their capacity to stain. The material submitted in table I strongly affirms the histochemical identity of megakaryocytic cytoplasm and platelets.

Megakaryocytic Nuclear Budding (Fig. 11)

Downey[17] observed in his early studies that the megakaryocytic nucleus gave off chromatic material to the cytoplasm and felt that this material was in some way associated with the development of cytoplasmic granules, Schwarz[21] felt that the bud-like excrescences of the nuclei were limited to seriously injured cells. Davidson and Smith[45] depicted a similar projection in neutrophilic leukocytes which was a manifestation of a structural difference in cells from the human female. Levy[26] proposed that disturbances of mitosis could lead to formation of small accessory nuclei which would have fewer chromosomes than the main nuclei.

Abnormalities in Thrombocytopoiesis in Pernicious Anemia

Although abnormalities in thrombocytopoiesis occur in many disorders of the marrow,[3,6,7,10,14,16,18,27,31,47,48] three types of such disturbances will be surveyed in this work because of the light they shed on the fundamental mechanisms of platelet formation. The first disorder to be considered is an investigation into the causes of the thrombocytopenia usually to be found in deficiencies of B_{12} leading to pernicious anemia. In the megakaryocytic series this deficiency leads primarily to disturbances of nucleoprotein synthesis. Gasper[46] noted that megakaryocytes were diminished in numbers and that their nuclei stained more intensely. Jones[47] confirmed these findings but in addition encountered pathologic megakaryocytes with intensely basophilic cytoplasm devoid of azurophilic granulation. Rohr[48] found similar cytoplasmic defects but was impressed by the marked nuclear segmentation. Paseyro[49] also described increased nuclear segmentation without separation. Japa[23] in contrast described an increase in his 2- and 4-nucleated stages and a marked decrease in megakaryocytes with 8 and 16 nuclei. Epstein[28] found 49.8 to 68.4% of the megakaryocytes in relapse to be multinucleated megakaryocytes (megakaryocytic polykaryocytes). After specific therapy only 0.0 to 11.2% of multinucleated megakaryocytes were present. In 4 out of 5 patients prior low platelet counts were increased and in 3 out of 5 patients remission brought about an increase in the number of megakaryocytes exhibiting apparent platelet formation. Pisciotta, Stefanini and Dameshek[14] using phase microscopy confirmed the earlier findings as seen with the light microscope. They commented on the "honeycomb" appearance of the nuclear chromatin characteristic of megaloblasts in some of the megakaryocytes before specific treatment was instituted. No platelet formation was found and the cytoplasm was either devoid of granules or granules were limited to the perinuclear area. In our own experience the basic defect is apparent in the disturbance of nuclear maturation. Hyperlobulation is present precociously in the pro-

megakaryocytic stage (Fig. 20); in addition there is abnormal retention of the fine, reticulated chromatin pattern of the nuclei even as late as the 8-nuclei stage. (Fig. 21) Excess number of multinucleated megakaryocytes as reported by Epstein[28] are present. (Fig. 21 and 22) Failure of normal nuclear growth and differentiation leads in turn to dissociation of development between nucleus and cytoplasm with subsequent inhibition of azurophilic granule formation, retention of primitive cytoplasmic basophilia and failure of platelet production.[50] Structural and functional integrity of the megakaryocytic system of cells has been accomplished within a week after institution of specific therapy.[14]

Abnormalities in Thrombocytopoiesis in Heat Stroke

Malamud and his associates[51] have uncovered an almost specific injury of the megakaryocytic series in heat stroke in man associated with temperatures above 106° F. Six hours after the onset of hyperpyrexia a reduction in numbers of megakaryocytes was visible. Severe damage of the nucleus was evidenced by pyknosis, karyorrhexis and disappearance of the nuclei before cytoplasmic dissolution.

Abnormalities in Thrombocytopoiesis in Idiopathic Thrombocytopenic Purpura

In idiopathic thrombocytopenic purpura (I.T.P.) of the chronic type megakaryocytes are usually paradoxically increased in numbers. Megakaryoblasts and promegakaryocytes are increased. Degenerated forms are increased but usually consist of degenerative changes in the afore-mentioned younger cells. Platelet productivity on the part of the megakaryocytes is significantly diminished. The numerous structural defects described in members of the megakaryocytic series of cells in I.T.P. can now be re-evaluated in the light of newer knowledge of the fundamental mechanisms of the disease by establishment of (a) the thrombocytopenic activity of plasma from patients with I.T.P. when injected into normal controls[52] and (b) megakaryocytic inhibition by potent platelet agglutinins in a patient with I.T.P. or induced in recipients with previously intact megakaryocytic systems by administration of such platelet agglutinins.[14,53]

Frank[33] early had described megakaryocytes in I.T.P. as possessing a hyoline cytoplasm, agranular and vacuolated. (cf. his Abt. 10, Fig. 3-6) These changes were reaffirmed by Limarzi and Schleicher[22] who reported in addition that many of the promegakaryocytes were forming nongranular pseudoplatelets. Dameshek and Miller[10] and Valentine[35] also described precocious nongranular platelet production by the promegakaryocytes but emphasized the marked reduction in platelet production from adult megakaryocytes. De La Fuente[27] after careful quantitation of this latter defect was able to state that in severe cases of I.T.P. mature or immature megakaryocytes containing more than 10 platelet units in their cell bodies were absent. Fig. 23 depicts a megakaryoblast in the marrow from a patient with I.T.P. The pseudopodial projections of the cytoplasm are a common finding in the increased numbers of this stage. The first azurophil granule have made their appearance near the nucleus. Fig. 24 is a promegakaryocyte from a similar patient. Azurophilic granulation is lacking. There is intense peripheral cytoplasmic vacuolation. Four large nongranular, vacuolated pseudopodia are present. Figs. 25 and 26 are adult megakaryocytes in the same condition. Fig. 25 shows unusual juxta-or intranuclear vacuolation. The large cell body is completely devoid of granules. An outer hyaline cytoplasmic zone is clearly

demarcated from the inner zone of abnormally deep basophilia, platelet formation is lacking. Fig. 26 depicts intense peripheral cytoplasmic vacuolation, presence of central azurophilic granulation, but the customary deletion of platelet productivity.

In the patient of Pisciotta and his associates[14] with a circulating high-titer platelet agglutinin the megakaryocytes showed generally intact nuclei, but there was pronounced vacuolization of the cytoplasm, with some cells showing peripheral "bare areas" and with little platelet formation in evidence. Two hours after the administration of the same plasma, the megakaryocytes of the recipients showed complete loss of platelet formation and some cells showed some loss of granule formation as well. Loss of granules was at times confined to the cell periphery. All megakaryocytes showed intense cytoplasmic vacuolation. Nuclear changes were minor. In such recipients the changes in the megakaryocytes were largely reversible. These findings suggest that in I.T.P. structural and functional defects in the megakaryocytes are brought about by direct injury to the cell. The increased proliferation of the younger forms would be compensatory in type. There remains unsettled the problem as to whether prolonged extrinsic injury of the cellular system ultimately can lead to intrinsic maturation defects. The demonstration of antibodies against nuclear materials, cytoplasmic organelles, and submicroscopic particulates in turn, as has been done for similar leukocytic components,[54] may render unnecessary further invocation of intrinsic maturation defects to explain megakaryocytic pathology in I.T.P.

Quantitative Studies of the Megakaryocytic System

Pizzolato[55] reviewed the literature of the many technics available up to 1948 for counting megakaryocytes. The results obtained varied greatly, chiefly because accurate total nucleated cell counts per unit of volume are not at present obtainable from the hematopoietic organs of man. Yoffey[56] has recently described a technic suitable for such quantitative total nucleated cell studies of the bone marrow in guinea pigs, but unfortunately this is not applicable to man. Semiquantitative methods in the hands of individual groups have shown a rewarding degree of reliability. Among such latter technics may be listed the thin-smear method of Dameshek and Miller,[10] the thick smear method of Osgood[57] and the various histologic section studies of Smith and Butcher[3] Berman[58] and Bowman and his associates.[59]

A Note on the Formation of Pathologic Platelets

From a consideration of the processes of normal and abnormal megakaryocytopoiesis as outlined in the preceding material, an understanding of many features of abnormal platelet formation can be obtained. Platelet release, before full granular aggregation has occurred, is the most common abnormality encountered and leads to the formation of large but otherwise unaffected platelets. Failure of regular hyalomeric cleavage may lead to release of pseudopodial forms in the case of pseudopodial production or to release of irregular undissociated platelet aggregates when production is by cytoplasmic disintegration. Nongranular platelets can be produced either by precocious production on the part of the megakaryoblasts and promegakaryocytes which cannot be expected to have attained their full component of granules or by pseudopodial formation on the part of older forms whose proper granulation has been inhibited or destroyed. Unduly basophilic nongranular forms with or without hyaline zones and vacuolation are the product of cells similar to those depicted in figs. 24 and 25. Platelet

release after complete granulation but before granular aggregation or hyalomeric cleavage (Fig. 12) can lead to either unusually large, completely granular, platelets or conversely very small ones, depending upon the size of the cytoplasmic fragments. For detailed descriptions and illustrations of these abnormal platelet products the reader is referred to work of Downey and Nordland.[7] Finally, the existence of normal platelet counts in man within fairly regularly assigned limits, implies the existence of a regulator or regulators determining megakaryocytic differentiation, maturation and platelet release.

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Table I

Histochemistry of Megakaryocytes and Platelets

	HISTOCHEMICAL TESTS																					
	Iodine 36	Best's Carmine 36	Bauer's 37, 38	Gomori 37, 38	Hotchkiss 36, 37, 38	Saliva + Hotchkiss 38	Sulfite blockade + Hotchkiss 38	Pyridine + Hotchkiss 38	Acetylation + Hotchkiss 38	Acetylation + KOH + Hotchkiss 38	Metachromasia 38	Plasmal reaction 39	Acid hematein 40	Pyridine Control 40	Sudan black B 40	Janus Green 40	Neutral Red 20, 40	Alkaline phosphatase 42, 43	Acid phosphatase 42, 43	RNA 44	Ribonuclease + RNA 44
Megakaryocyte Cytoplasm	+	+	+	+	+	+	+	+	−	+	−	+						±	+	+	−
Granules			+	+	+	−	+	+	−	+	−		+	−	+	+	+				
Inclusions			+	+	+	−	+	+	−	+	−										
Nucleus													−	+				+	+		
Nucleoli																		+	±		
Platelets	+	+	+	+	+	−	+	+	−	+	−	+	+	−	−	+	+	+		±	

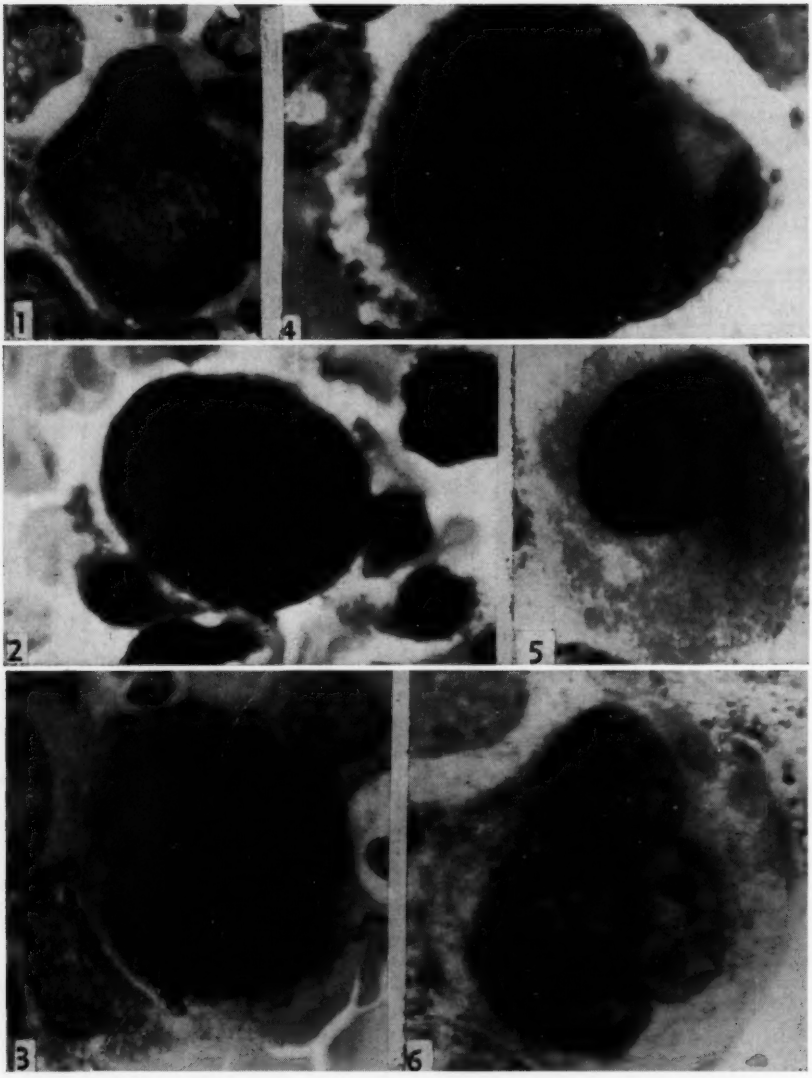


Fig. 1. Megakaryoblast; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000 AFIP Neg. 96993.

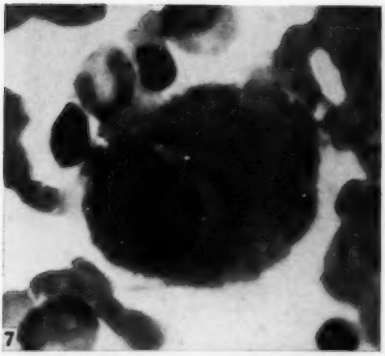
Fig. 2. Megakaryoblast; bone marrow aspirate. May-Grunwald Giemsa stain. x 1800.

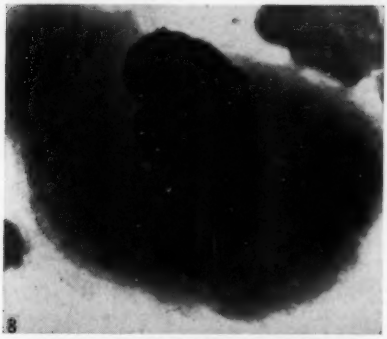
Fig. 3. Megakaryoblast; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

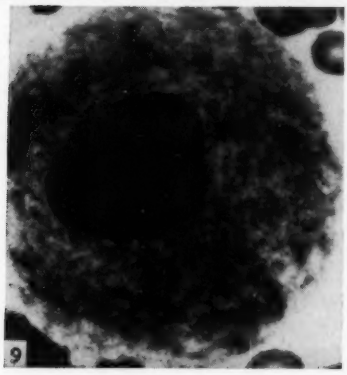
Fig. 4. Late megakaryoblast, granulation at right of nucleus; bone marrow aspirate. May-Grunwald Giemsa stain. x 1800.

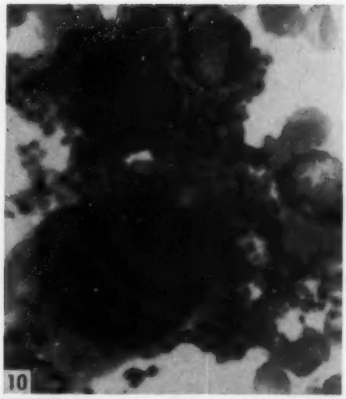
Fig. 5. Promegakaryocyte; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000. AFIP Neg. 97006.

Fig. 6. Promegakaryocyte; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000. AFIP Neg. 97005.









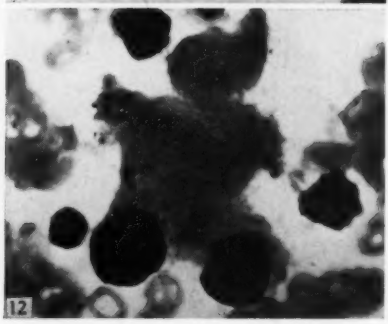


Fig. 7. Late promegakaryocyte (intermediate form). Bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

Fig. 8. Adult megakaryocyte; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

Fig. 9. Mature megakaryocyte showing granular aggregation; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000. AFIP Neg. 98047.

Fig. 10. Megakaryocyte showing platelet formation; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

Fig. 11. Megakaryocytic nuclear budding; bone marrow aspirate. May-Grunwald Giemsa stain. x 1800.

Fig. 12. Multinucleated megakaryocyte; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

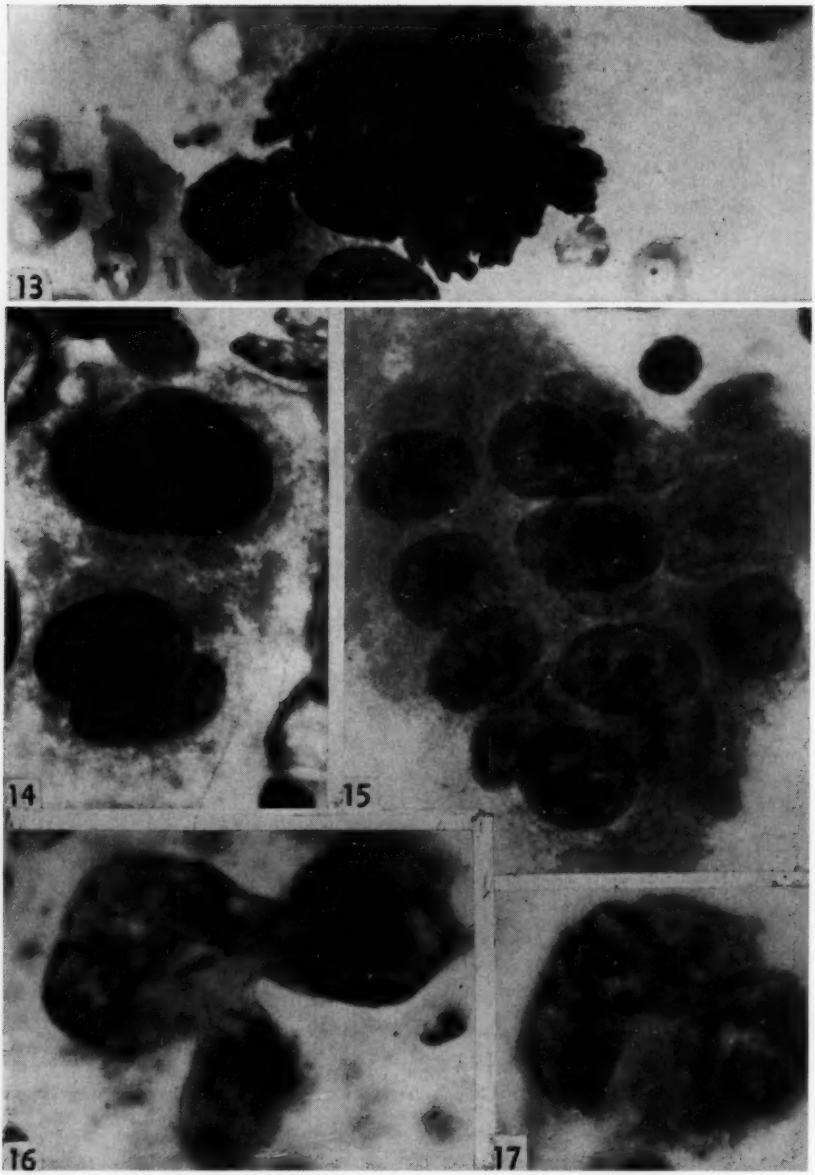


Fig. 13. Multipolar mitosis in developing megakaryocyte; bone marrow aspirate. May-Grunwald Giemsa stain. x 1550. Fig. 14. Multinucleated megakaryocyte; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000. AFIP Neg. 96991. Fig. 15. Osteoclast; sternal bone marrow aspirate. May-Grunwald Giemsa stain. x 2000. AFIP Neg. 98023. Fig. 16. Leukemic megakaryocyte. Section of spleen in megakaryocytic leukemia. Hematoxylin and eosin stain. x 2000. AFIP Neg. 97896. Fig. 17. Leukemic megakaryocyte. Section of bone marrow in megakaryocytic leukemia. Hematoxylin and eosin stain. x 2000. AFIP Neg. 97604.

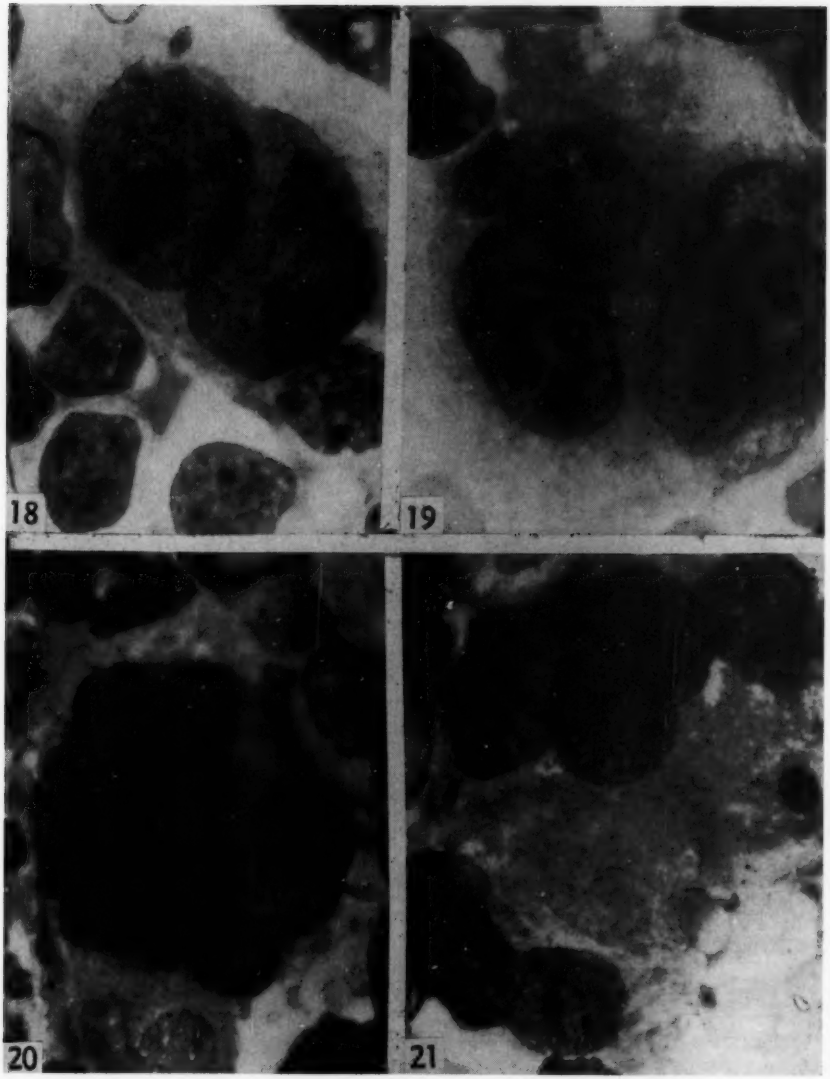


Fig. 18. Small Reed-Sternberg cell. Imprint of lymph node in Hodgkin's disease. Wright-Giemsa stain. x 2000. AFIP Neg. 98050.

Fig. 19. Reed-Sternberg cell. Imprint of lymph node in Hodgkin's disease. Wright-Giemsa stain. x 2000. AFIP Neg. 97901.

Fig. 20. Hyperlobulation of nucleus in promegakaryocyte of pernicious anemia; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

Fig. 21. Failure of nuclear maturation in promegakaryocyte of pernicious anemia; bone marrow aspirate. May-Grunwald Giemsa stain. x 1550.

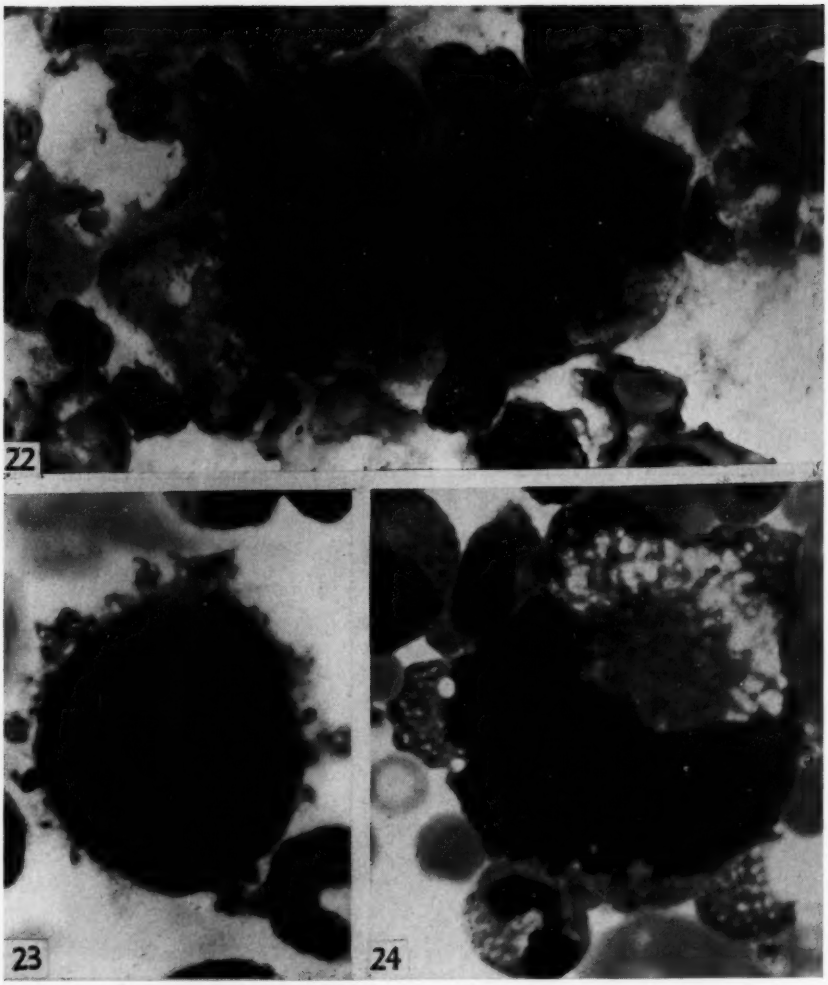


Fig. 22. Multinucleated megakaryocyte lacking platelet formation in pernicious anemia; bone marrow aspirate. May-Grunwald Giemsa stain. x 1550.

Fig. 23. Megakaryoblast showing precocious platelet formation in ITP; bone marrow aspirate. May-Grunwald Giemsa stain. x 1900.

Fig. 24. Promegakaryocyte, agranular with peripheral vacuolation in ITP; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

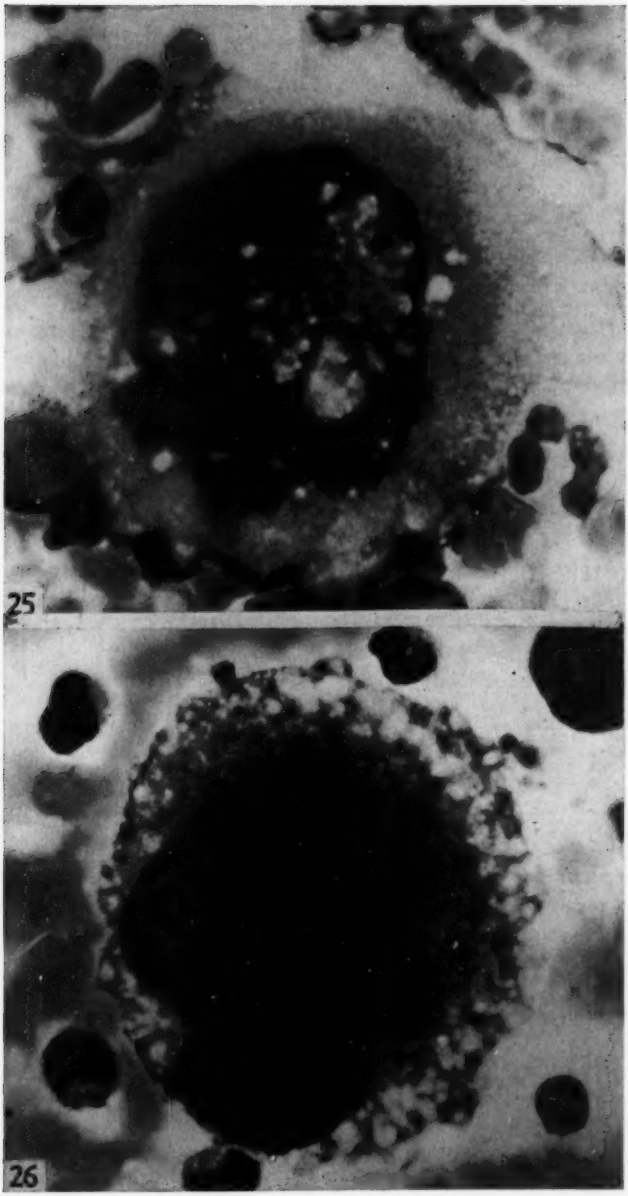


Fig. 25. Megakaryocyte, agranular with perinuclear vacuolation and lacking platelet formation in ITP; bone marrow aspirate. May-Grunwald Giemsa stain. x 1500.

Fig. 26. Megakaryocyte with peripheral vacuolation and lacking platelet formation in ITP; bone marrow aspirate. May-Grunwald Giemsa stain. x 1800.

THE MARFAN SYNDROME
A Report of an Atypical Case

WILLIAM H. HOUSTON, M.D.*

K. G., a 14 year old colored male, was first seen in the Henry Ford Hospital in September, 1956, by the Pediatric Department. He was brought in primarily for evaluation of his general physical condition, especially in regard to a spinal curvature.

Past History: The patient was normal full term child born following an uneventful pregnancy and a normal labor. His general health has been excellent.

Family History: There were three fairly tall maternal uncles but none with a body habitus similar to the patient's. No relatives have died suddenly or have other symptoms suggestive of a dissecting aneurysm. The father has bilateral cataracts which began at the age of 25. The patient has two normal siblings.

Pertinent Physical Findings: Height 176 cms. with an arm span of 196 cms. Weight 107 lbs. His head was somewhat tower-shaped (Fig. 1). There was a pronounced arachnodactyly and his extremeties were long and narrow, his fingertips reaching the knee level when he was standing erect (Fig. 2). There was a pronounced kyphoscoliosis with an associated thoracic cage asymmetry (Fig. 3). He showed none of the features usually seen in the typical Marfan syndrome, such as under-development of the muscles, sparsity of the subcutaneous fat, laxity of joint capsules and flat feet. Evaluation by the Cardiology Department showed no abnormalities. Mental development was normal.

Eye Examination: There was some slight facial asymmetry, the right eye being 3 mms. higher than the left and the right palpebral fissure being slanted slightly upward The corneas were clear. The pupils were round, regular, of equal size and reacted normally to light and accommodation. Visual acuity without correction: RE 20/30-2, LE 20/15.

Muscle balance without correction:

DV: 4 prism diopters of intermittent esotropia.

NV: 3 prism diopters of intermittent esotropia with 2 prism diopters of left hyperphoria.

Fixation with the left eye was preferred. Extraocular movements were normal. Near point of convergence was 3 cms.

Manifest refraction was unsatisfactory.

Cycloplegic refraction: RE: $-.25 + .75 \times 90 = 20/30$

LE: $+.25 + .25 \times 180 = 20/15$

Slit Lamp: Both corneas were clear. The anterior chambers were deep, well-formed and optically empty. The irides were normal. The lenses were of normal transparency and in normal position. There was a fine vitreous haze in the right eye. The vitreous in the left eye was normal.

*Department of Ophthalmology.

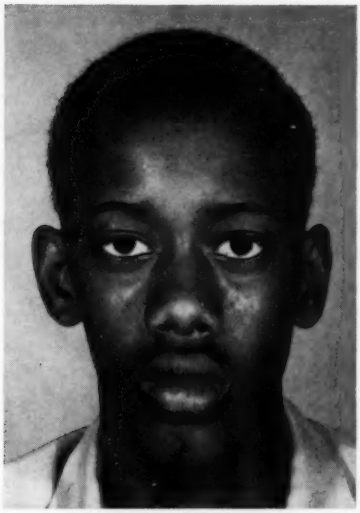


Fig. 1. Tower Shaped Head

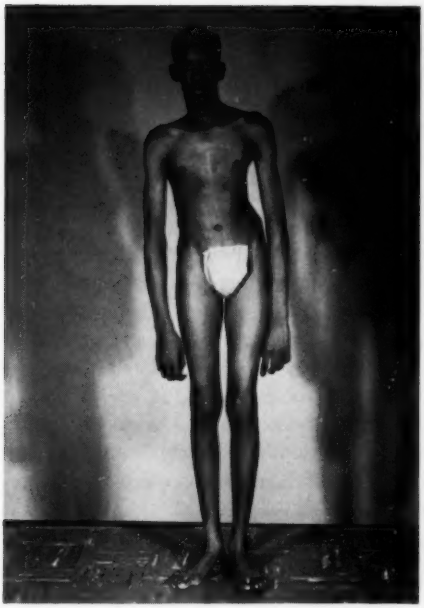


Fig. 2. Long Narrow Extremities

Fig. 3 Kyphoscoliosis with associated Thoracic Cage Asymmetry

Ophthalmoscopic examination: No abnormalities were observed.
Visual Field examination: Full peripherally to the 3/330 white isopter. The red isopters, centrally, were likewise normal with the exception that in the right eye the 2 mm. red isopter did not appear to be quite as red at the point of fixation as it did about 2 degrees out. This is interpreted as being a partial scotoma to the 2 mm. red isopter from suppression amblyopia.
Tension: RE 17 mm. Hg.
LE 17 mm. Hg.

Classification of this case with respect to Marfan's syndrome involves some speculative aspects. A brief review of the Marfan syndrome therefore seems in order.

I. *Clinical Manifestations.*

The individual with Marfan's syndrome shows a typical body habitus consisting of long thin extremities. In general, the more distal bones of the extremities tend to demonstrate this excessive length more strikingly. Arachnodactyly is the result. The affected individual tends to be tall. Redundancy and weakness of joint capsules, ligaments, tendons and fascia are responsible for a large group of disorders which include pes planus, genu recurvatum, hyperextensibility of joints, habitual dislocation of the hips, patella, clavicles, mandible and other joints. Ganglia, hernias, synovial diverticula and kyphoscoliosis are also seen frequently. The skull and face bones are long and narrow with a resultant highly arched palate and prognathism. Muscular underdevelopment and hypotonia along with a pronounced sparsity of subcutaneous fat is a prominent feature.

The cardiovascular system is strikingly involved. An abiotrophy of the elastic tissue of the aorta and pulmonary artery may result in a diffuse dilatation of these vessels or in a dissecting aneurysm. This latter development has resulted in the early death of many individuals with this syndrome.

The eye — Ectopia lentis, almost always bilateral, is the hallmark of ocular involvement. Seventy percent of all cases of congenital ectopia lentis occur as components of the Marfan syndrome. The zonules, when visualized with the slit lamp, are redundant, attenuated and often broken. The lower ligaments are most often defective with a consequent upward displacement of the lens. The lenses are often small and may be spherical. Coloboma lentis has been reported. Secondary iritis and glaucoma often occur. Axial myopia is usually present and has been reported to be as high as twenty diopters in some cases. This tends to indicate involvement of the sclera, fundamentally a ligamentous structure, in a basic connective tissue defect. The scleral defect is occasionally expressed in the cornea as keratoconus, clouding or megalocornea. The sclera may be impressively blue. The pupil is often difficult or impossible to dilate due to hypoplasia of the dilator pupillae muscle.

Spontaneous retinal detachments occur in unusually high incidence and are a frequent complication of lens extractions. Severe limitation of visual acuity and even total blindness occurs all too frequently.

Some patients with advanced Marfan's syndrome, familial in that other members of the family were involved, and with characteristic body habitus, dissection of the aorta, and autopsy demonstration of the pathognomonic changes in the media, have

not shown ocular abnormalities even on the most careful examination. This part of the syndrome, it seems, may be repressed completely in a given family.

II. *Differential Diagnosis.*

In the Negro race particularly, the Marfan syndrome is often suggested by the skeletal proportions. A picture mimicking it in many respects can result from Rh incompatibility or from intra-uterine rubella infection. Ectopia lentis does not occur in these cases. Arachnodactyly *per se* is not to be taken to indicate Marfan's syndrome as it is a nonspecific manifestation with many possible causes. Atypical muscular dystrophys can be confused with Marfan's syndrome and may require histological differentiation. Given stigmata suggestive of the Marfan syndrome, one can be most confident of the diagnosis if ectopia lentis is present in the patient or if other members of the family are unequivocally affected.

III. *Incidence and Inheritance.*

The sexes are equally affected. There is no racial or subracial concentration of cases. It has been reported from all parts of the world. It is an uncommon but by no means rare disease. The connective tissue defect involving the aorta is the leading cause of dissecting aortic aneurysms in the younger decades. There is reason to believe that there is an appreciable number of very mild or *forme fruste* cases in which the connective tissue defect has little effect on the health and longevity.

Partial submersion of the manifestation of this syndrome can be observed in pyknic stock; the individuals thus affected may not have an impressively unusual habitus. However, no protection from ocular or aortic abnormality is afforded thereby.

The pattern of inheritance is that of a simple Mendelian autosomal dominant. Parenteral consanguinity has not been an impressive feature. Sporadic *de novo* mutations arise in perhaps 15% of all cases.

IV. *Pathology.*

The basic defect is an abiotrophy of the elastic tissue fibers. They are constitutionally inadequate and undergo degeneration, particularly at sites of stress, the ascending aorta, for instance. The smooth muscle elements, which normally originate and insert on the elastic lamellae, collapse together into disorganized whorls and undergo hyperplasia and hypertrophy. Reparative processes leave the tissues scarred and weakened. Exactly what the zonule of the lens has in common with the elastic tissue of the media of the aorta is unknown. If it were known, the basic defect might be better understood.

Comment.

The physical features in this case are compatible with a mild form of the Marfan syndrome, but the eyes showed none of the typical manifestations. However, as mentioned previously, the ocular abnormalities may be completely suppressed in certain cases. Our tentative diagnosis is: *Forme fruste* Marfan's syndrome, *de novo* mutation.

Summary.

A diagnostic problem concerning a questionable case of Marfan's syndrome is presented. The clinical manifestations, differential diagnosis, incidence, heredity and pathology of the Marfan syndrome are reviewed briefly.

BETA-PROPIOLACTONE FOR THE STERILIZATION OF BIOLOGICAL MATERIALS

GERALD A. LOGRIPPO, M.D.*

INTRODUCTION

Although the sterilization of biological materials has been widely used for many years, the agents employed are still not entirely satisfactory. Moreover, the scope of biological materials which can be sterilized has been limited. Heat, ultraviolet irradiation, formalin and phenol have been the most commonly used agents for sterilization. However, with these agents there is a rather marked alteration of protein material with the loss of the biological characteristics necessary for clinical usefulness. In addition, in recent years the problem of virus contamination has been brought to the attention of the clinicians more forcibly than ever before. This has been further complicated by the fact that the bactericidal agents in common use destory the biological material before they effectively inactivate the viruses. This has been true in the sterilization of plasma where there has been no satisfactory means of destroying the hepatitis virus, an increasing hazard in the use of transfusions.[1,2] More recently Beutler and Dern[3] have demonstrated another virus agent that is transmitted from the blood of healthy donors to recipients.

It is known that at least 16 viruses, infectious to man, can produce a viremic phase. How many of these agents persist in the *"carrier stage"* in man is difficult to prove with our present laboratory technics. Although the technics are not sensitive enough to detect the trace quantities that may persist, these trace quantities are sufficient to transmit the disease to susceptible human hosts whenever blood, blood products or homologous tissue are used in man. With the increasing use of biological materials of human origin being used in man, sterilization of these products *must be* insured not only from the bacterial agents but also from all of the microbiological pathogens.

Beta-propiolactone (BPL) has been reported from this laboratory as a more satisfactory sterilizing agent[4,5,6,7,8,9] against viruses, bacteria, fungi, spore forms of bacteria and fungi and malignant cells. Moreover, sterilization can be obtained at drug concentrations which are not deleterious to tissue proteins. BPL has been successfully developed and employed in several different clinical problems involving the use of biological materials. These are (1) the sterilization of human plasma, (2) the establishment and operation of a human tissue bank and (3) the preparation of inactivated virus vaccines.

BETA-PROPIOLACTONE

The chemical agent, beta-propiolactone (BPL) $CH_2CH_2C = O$, is a colorless stable liquid in its concentrated state but is unstable in aqueous solutions. It can be satisfactorily stored in plastic containers or in neutraglass sealed ampules at -20 to -30 degrees centigrade. BPL has a specific gravity of 1.149 and is 37.5% (by volume)

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soluble in water at 25° C. It reacts readily with hydroxyl, amino, carboxyl sulfhydryl and phenolic groups,[10,11,12] all of which are associated with proteins.

The instability of the chemical structure of beta-propiolactone accounts for its unavailability in the past. Although the agent was known to exist in 1885, it was not until 1915 that Johannson[13] actually prepared the agent. In 1941, Kung[14] found a practical method for the manufacture of beta-propiolactone. After sitting on the shelves of the organic chemists for nine years with no practical use for the compound, it was tested for its virucidal action in plasma during a routine screening program conducted in this laboratory. The recent synthesis of the lactone form made possible an extensive study of reactions of the drug with biological materials for *sterilization of plasma, tissues* and *the preparation of inactivated virus vaccines.*

STERILIZATION OF HUMAN PLASMA

Previous publications give in more detail the superiority of BPL over nitrogen mustard, sulfur mustard, ethylene oxide, photodynamic action of dyes and ultraviolet irradiation for the inactivation of numerous viruses artificially seeded in plasma and those naturally occurring in plasma during the stage of viremia.[5,6] Extensive studies from this laboratory also show that a wide margin of safety exists between the virucidal concentrations[15] of beta-propiolactone and the toxicity concentrations[16,17] of beta-propiolactone. However, since the hepatitis virus is not an agent which can be yet studied in the experimental laboratory, the effectiveness of beta-propiolactone upon this agent remains to be answered in human volunteers. Although plasma treated with 0.6% beta-propiolactone concentration is not toxic to man upon intravenous administration, this concentration is 1.5 times that necessary to inactivate the most resistant laboratory virus (eastern equine encephalomyelitis) and 12 times that necessary to inactivate the most sensitive virus (lymphocytic choriomeningitis) when these agents are seeded in plasma. However, in order to maintain the integrity of the fibrinogen in plasma, a concentration of 0.45% beta-propiolactone should not be exceeded. Since this concentration is only slightly in excess of that necessary to inactivate the most sturdy laboratory viruses, it may not be sufficient to inactivate the trace quantities of hepatitis virus that may be theoretically present. For these reasons, the combination of beta-propiolactone and ultraviolet irradiation previously reported[5] was more extensively studied.[18,19,20,21,22]

Animal experimentations with the eastern equine encephalomyelitis virus (EEE) clearly show that there is always an additive and often a synergistic virucidal effect with beta-propiolactone and ultraviolet irradiation.* The same degree of virus inactivation (i.e., nondetectable quantities) can be obtained in combination with 1/3 to 1/4 the beta-propiolactone concentration and 1/3 to 1/4 the ultraviolet irradiation than when either agent is used alone. What is more important is the fact that the combination can be used in marked excess of that necessary for sterilization and still maintain the integrity of the fibrinogen and other plasma proteins as demonstrated by electrophoretic patterns. With a wider range between sterilization dosage and protein alteration, the combination here shown stands a greater chance of inactivating the hepatitis virus in human plasma.

Plasma treated with 0.35% beta-propiolactone and ultraviolet irradiation intensity recommended and used by the National Institute of Health Standards produces a

*(The Dill ultraviolet apparatus was used for these studies).

product which is clear and amber in appearance, stores well at refrigerator temperature, and is well tolerated by patients. Over 100 units have been administered to infants and adults without any clinical pathological manifestations.

ESTABLISHMENT AND OPERATION OF A HUMAN TISSUE BANK

With the ever increasing demand for sterile tissue transplants in the field of surgery and with human autopsy material being the most likely source for an adequate supply of homotransplants, a simple, inexpensive and safe procedure for sterilizing tissue is greatly needed. The usual practice of testing for bacterial and mycotic contamination overlooks the potential hazards of virus infection, malignant growths and parasites. It is possible with the use of beta-propiolactone to completely sterilize tissue supplied from autopsy material and thus establish a human tissue bank. Such a bank has been in operation at the Henry Ford Hospital for three and one-half years.

The human arterial bank was first established in October 1953, having been preceded by study of arterial transplants in dogs.[23] These experiments were initiated by Dr. C. Lam and associates in Surgery with the cooperation of the Department of Laboratories.[7,8] After two years work, the results in dogs were concluded to be highly satisfactory, and it was felt that trial of homologous grafts in man was justified. The clinical trial was carried out by Dr. D. E. Szilagyi[24,25,26,27] and associates in the Department of Surgery with the cooperation of the Department of Laboratories.

The tissue bank operates in the following manner:

1. A special permit for the procurement of human arteries is necessary. This is easiest to obtain from the family at the time the autopsy permit is being signed. In obtaining the arteries, no exceptions are made regarding age and cause of death.
2. A surgical resident is charged with the responsibilities of obtaining, preparing, discarding poor segments, classifying and recording data pertaining to the arteries.
3. The arteries are obtained without aseptic precautions and sterilized within 24-36 hours from time of death, without elaborate procedures or inconvenience to any one concerned.
4. The sterilization and completion of the sterility tests are the responsibility of a bacteriology technician. The tissues are then returned to the respective surgical services for storage.

Two-hundred and sixty-eight operations have been performed with beta-propiolactone sterilized arteries by the Department of Arterial Surgery. In no case was there evidence of failure being due to inadequate sterilization, nor has there been any evidence of infection, either bacterial or viral. After successful sterilization of arteries and acceptance by the host, sterilization studies were extended to bone tissue with the cooperation of Dr. C. L. Mitchell and Dr. J. Fleming, Department of Orthopedic Surgery.

The bone bank was established in July 1955, again placing a resident in Orthopedic Surgery in charge of the preparation of the bone segments in the sizes and shapes desired by the surgeons. Usually ribs, iliac crest and vertebral bodies afford an ample supply of cancellous and cortical bone without special permits. To sterilize bone it

is important to remember that segments can be as long and as wide as the surgeon wishes, but they cannot be greater than 6 mm. thick. This maximum thickness was determined by experimental data obtained with bone pieces varying in thickness from 1-2-3-6-9 and 12 mm. sizes. These were contaminated in bacterial broth suspensions for 18 hours before sterilizing with the beta-propiolactone. In addition, varying thicknesses obtained from infected rabbits and guinea pigs during the stage of bacteremia and viremia were sterilized.[9] All specimens were consistently sterilized at 6 mm. thickness. Sterilization at 9 mm. thickness is inconsistent.

After sterilization the bone can be kept frozen at —20 to —30° C. in an ordinary deep freeze unit, or lyophilized (freeze-dried) and stored at room temperature in vacuum. The clinical results of beta-propiolactone sterilized bone have been very satisfactory.

As of March 1, 1957 specimens from the BPL treated bone bank have been used in 70 operations. The procedures have included filling of large cysts, spinal fusions for tuberculosis and scoliosis, grafting of fractures both fresh and old, and for various other fusions. Only one infection was noted in this series (open reduction of os calcis fracture with skin slough and infection on the 13th postoperative day). However, this case healed without losing the graft or the reduction.

More recently sterilized skin and cartilage have also been used with the cooperation of Dr. R. H. Clifford and Dr. W. D. Butt, Department of Plastic Surgery. However, this is still in the early trial stage. Sufficient evidence has been collected to say that beta-propiolactone sterilized, homologous, skin grafts are as serviceable as the nontreated, homologous, skin grafts, without the complication of infection. The rejection period is the same as that of the nontreated, homologous, skin grafts.

The results with cartilage, again few in number, indicate that sterilization is satisfactory. The cartilage transplants occasionally resorb as do fresh autogenous transplants or nonsterilized, refrigerated, homologous transplants. When resorption takes place the reaction is slow with no evidence of toxic or inflammatory reactions.

In conclusion, it can be stated that, with the use of beta-propiolactone as the sterilizing agent, a tissue bank can be established in a hospital of any size with a minimum of equipment and no need for highly skilled technical assistance. At the present time, establishment and operation of a tissue bank is most useful for the preparation and storage of sterile, homologous, arterial, bone, cartilage and skin transplants.

ANTIGENICITY OF BETA-PROPIOLACTONE INACTIVATED-VIRUS VACCINES

In the preparation of inactivated virus vaccines, the margin of safety between complete virus inactivation and the degree of antigenicity retained is so narrow that a search for a more satisfactory agent has not abated.

In previous reports[28,29] and in studies in progress, beta-propiolactone seems superior to other chemical agents for the preparation of inactivated virus vaccines. It inactivates viruses completely and irreversibly in 10-15 minutes at 37° C. whereas formalin and phenol require days under the same conditions. The beta-propiolactone concentration can be added in excess of the minimal effective virucidal concentration with

a wide margin of safety between the complete inactivation of viruses and loss of antigenicity. Moreover, significantly higher degrees of antigenicity have been obtained with beta-propiolactone inactivated-virus vaccines than with phenol — or formalin — inactivated vaccines under parallel conditions. The vaccine preparations were made with rabies, eastern equine encephalomyelitis, murine (MM-strain) encephalomyocarditis and poliomyelitis viruses.

Upon demonstration by animal experimentation of the superiority of beta-propiolactone inactivated virus vaccines, human trials with such preparations have begun. Peck, Powell and Culbertson,[30,31] from the Lilly Laboratories for Clinical Research, Indianapolis General Hospital and the Lilly Research Laboratories, have recently prepared and clinically tested a beta-propiolactone killed rabies vaccine with good results in man. The rabies vaccine was prepared from embryonated duck eggs in place of the conventional rabbit brain material. The absence of brain tissue in this preparation and the appearance of detectable antibodies between 7 and 10 days after the first inoculation indicate marked improvement in the methods of immunization against rabies.

SUMMARY

Beta-propiolactone, a new chemical agent, has been demonstrated to be a useful substance in the sterilization of biological materials. Its unique properties, not available in other agents used for treating biological material, have made possible the treatment of human plasma for the inactivation of viruses, without destroying the usefulness of the product for clinical use. Beta-propiolactone has made possible the establishment of an inexpensive and practical tissue bank by successful sterilization of contaminated tissue from autopsy material without destroying the properties of the transplants for clinical use. In addition, beta-propiolactone is finding its place in the preparation of safer and more potent inactivated virus vaccines.

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MEDICAL EDUCATION AND PRACTICE IN GERMANY

NIELS R. WAEHNELDT, M.D.*

The German school and university system is based upon a unified and coordinated curriculum; i.e. it permits every child and every student to change high school or university in the different parts of Germany without any loss of time. The only difference between the schools is the quality of teaching within the different subjects. The pride concerning the tradition of an old school is not always justified when it comes to quality; in other words, the well-known name of a school or university does not guarantee quality.

There are 20 universities in Germany which maintain medical faculties.** The number of medical students enrolled in these faculties ranges from 30 to 150 per class. It was extremely difficult to gain admission to the medical faculties during the recent post-war period between 1946 and 1948. Required were certain good marks in the final examination of the high school, the so-called "Abitur" which is the outstanding examination in all German educational systems. At the present time, the largest medical faculty, as well as university, is Munich, whereas the smallest is probably Erlangen. Admission to the faculties does not necessarily guarantee graduation. During World War II, the number of medical students was much higher because of the great number of casualties among physicians.

The training in German medical faculties includes 2½ years of preclinical instruction and 3 years of clinical training. After the preclinical phase, a set of examinations, known as the "Physikum", determines the students competence to continue with the clinical phase of his training. At the end of the clinical phase, the student receives another set of examinations, known as the "Staatsexamen", recognized as a qualifying examination throughout Germany. The successful completion of this examination, together with a one-year internship as well as a three months praeceptorship under a general practitioner in a rural district, permits the candidate to practice legally as a physician.

The preclinical phase consists of courses in anatomy, histology, embryology, physics, chemistry, zoology, botany, physiology, biochemistry, and history of medicine.

The clinical training covers internal medicine, surgery, pathology, bacteriology, pharmacology, forensic medicine, otology, laryngology, ophthalmology, pediatrics, psychiatry, neurology, gynecology, obstetrics, orthopedics, urology, radiology, and public health.

The heart of the medical curriculum is the lecture and the lecture-demonstration taking place during the actual semesters (two per year). It is usual that the professor gives the complete series of the didactic lectures in his department, and these are supplemented by a series of lecture-demonstrations given by the chief-lecturer. An

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**The term medical faculties as used means the entire medical school, students, teachers and organization.

advantage of the German system of having the lectures given by the professors rather than by the specialist, who likely knows more about a particular subject than his chief, is that the lecture is apt to be well given. A good lecturer will draw students to his university. Hence, it is a general policy that the student is encouraged not to stay in one university but to move from one to another.

The object of the clinical years appears to be for the student to learn about disease largely by lecture and demonstration. It includes training in direct patient contact, predominantly during vacation as "famulus"*. Students are keen to get the best "famulus" assignments possible, knowing full well the value of the experience it represents. It is customary to spend about 10-12 months as "famulus" in teaching hospitals.

The decision of when one is ready to practice is left to the student, not the faculty, since the profound high school experiences enable the student in Germany to approach problems by himself. At the universities, there is no place for a "spoon-feeding" type of teaching. The academic freedom, a factor that dates back to the Middle Ages, guarantees the right to study what one wants to. Anyone who passes the "Abitur" which, as aforementioned, is the difficult final examination from high school, is ready to enter medical school.

Upon completion of the 5½ years training, including the "Staatsexamen", a dissertation about an experimental or statistical problem in medicine under the supervision of a department chief has to be written in order to receive the title "Doctor of the entire Medicine". But this is not the end of the road which enables the German physician to open his office after the completion of all the different requirements.

The insurance system founded by Bismarck in 1882, (A.O.K.) is the central core of the practice of medicine in Germany. There are about 8,000 doctors waiting their time for approval to practice in the system. The waiting period generally is about 5 to 8 years or even more after the completion of intern training. During this very inconvenient waiting period, the majority take residencies in the different branches of medicine. Since about 87% of the people come under the privately administered but legally compulsory insurance system, a physician, especially the general practitioner, can scarcely carry on without the backlog of money from this system. This system has not been revised since 1924, save in minor respects. The fee for a practitioner's care for a patient for three months is about 5 or 6 marks, with 3 marks for a home visit, extras for injections and special procedures and about 35 marks for a home delivery and 25 marks for an appendectomy. The amount paid in any area is constant for each quarter and is divided according to the amount for work done, so that in times of increased sickness, the fees go down. The people complain that there is no more money available for medical costs since the total compulsory payment by workers for medical, old age, unemployment and other insurance and for taxes amounts to about 33% of the take-home pay. If there is objection on the part of the physicians to the low fee schedule or other factors, the insurance companies readily point to the surplus of doctors eagerly waiting their turn for approval.

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*Famulus—Attendant or assistant

Ill patients and the majority of maternity cases are sent to the hospital, where the insurance system continues to pay. For hospitalized patients, another group of physicians, on full-time status, assumes the care. One of the shortcomings in the system is that there is no provision under the insurance system for preventive and prophylactic medical care; in other words, the insurance system pays for treatment but not prevention.

In regard to the insurance system itself, apart from its effect on medical care as a whole, much remains to be said. But one final important point should be made: the insurance system is often abused by the unscrupulous patient because it is free, a condition that exploits the doctors and demoralizes the people.

HELPING THE HEARING IMPAIRED TO ACHIEVE BETTER ARTICULATION*

MARY ROSE COSTELLO, Ph.D.**

Speech and articulation are terms which refer to the expressive aspects of the complex language skills of man. Speech which is used for the expression of ideas is closely related to and dependent upon the comprehension of language and upon inner language or thinking. A delay in any aspect of language growth may result from psychological, neurological, or physiological disturbances. Anyone of these conditions may disrupt the communicative system relied upon for the reception or expression of speech. If such a communicative breakdown occurs early in life, before speech is established, a child will exhibit a disorder in expressive language (speech) or receptive language (comprehension) or both.

An impairment in hearing is a breakdown in the receptive part of the communicative mechanism. It impedes or prevents the reception of the acoustic speech stimulus. When this impairment is present from early life, the effects upon language usage are not confined to the comprehension of speech, but retard also the growth of verbal language used for thinking and for expression. The development of intelligible speech for the hearing impaired hinges upon a recognition of the fundamental role of speech reception in normal speech growth, of the inter-relationship of the expressive, receptive, and inner language processes, and of the compensatory behavior necessitated by a defective receiving system.

Intelligibility of speech is not simply a function of the precision with which speech sounds are articulated. It is related to the voice quality, speech rate, intonation patterns and to the clarity and conventionality with which the individual puts words together for the expression of ideas. Each of these features of speech may be deviant when a child has a critical loss of hearing from early life. These characteristics are a natural outgrowth of the way in which he perceives the speech of others, and of the way in which he monitors his own speech.

In order for an individual with a critical defect in hearing to comprehend speech, a partial or total shift to a visual communicative system is necessitated. Lipreading supplements the perception of the acoustic speech pattern or may, in instances of profound deafness, serve as the primary receiving method with acoustic patterns serving as alerting devices. Unfortunately visually perceived speech possesses serious limitations particularly in the language developmental period. Vision, being a directional sense, limits speech experience to a marked degree. Unlike the hearing child who cannot shut out speech coming from in front, behind, or the sides, the deaf or severely hard of hearing experience spoken language only when their attention and eyes are focused upon the speaker. In addition lipread-speech does not provide an accurate visual reproduction of the speech pattern. Many speech sounds are not visible, several

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**Section of Audiology.

cannot be discriminated from each other, and there are countless words and expressions which present similar difficulties. Moreover, visually perceived speech does not depict as adequately the particular emphases and intonations which voice changes convey so readily.

These inadequacies in visually perceived speech are reflected in vocabulary deficiencies and in immature sentence structure. The child tends to imitate the visually perceived speech pattern, consequently numerous words and sounds are omitted or distorted. The hard of hearing or deaf voice lacks the expressive intonational changes which the hearing person so readily acquires through the hearing and imitating of others. The greater the dependence upon vision, the greater the retardation will be in the development of expressive language.

Speech intelligibility for the hearing-impaired is further reduced because of another aspect of the auditory impairment. Hearing not only acts as a distance sense providing us with information about the surrounding environment, it also informs us continuously about our own body sounds. Of foremost importance is the control it exercises over speech. Hearing guides and corrects speech efforts until they approximate the accepted standard. We match our own inflectional patterns to those used in our speech environment. We correct for too great or too little intensity. This auditory feed-back mechanism, when defective, must be replaced or supplemented by tactile, kinaesthetic and vibrational cues. But, like the compensatory use of vision for the reception of speech, these sensory stimuli have marked limitations for the monitoring of speech.

The chief limitation lies in the absence of an adequate speech model for the child to imitate. The reproduction of the auditorally and visually perceived aspects results in the defective speech typical of the hearing impaired. To produce good speech the child must add to and change the pattern he receives. Sounds which cannot be perceived must be interposed. Those which are distorted must be modified. Sounds and words, which appear identical visually, must be produced in a distinguishable manner. In order to do this experience must be had with a speech pattern which possesses good intelligibility. This experience can be provided only by the hard of hearing child himself. His own speech efforts under the direction of a speech therapist gradually approximate the accepted standard and supply the needed experience. The therapist presents speech to the child through the simultaneous stimulation of audition, vision and if necessary, touch. In the initial stages she corrects and modifies the child's efforts on the basis of the acoustical results. When a satisfactory reproduction is achieved, varied opportunity is provided so that the child may learn this pattern and be able to produce it at will. The memory of the sensation patterns resulting from speech sound production will then serve as the censor or monitor of future efforts. Inextricably interwoven with the sensory monitoring system is the child's knowledge of vocabulary, meaning and sentence structure.

The limitations of such speech reception and monitoring indicate that the correction or development of speech is not a simple matter of teaching the child how speech sounds are articulated. It involves consideration of the problems brought about by limited speech experience and by the shifted method of speech control. It requires the establishment and consistent use of the most efficient systems available.

Hearing and Articulation

Research has shown repeatedly that the maximal use of hearing contributes both to the improved speech comprehension and speech production. Fortunately for the majority of children hearing can make up an important part of the receiving and monitoring processes. In order for the auditory potential to be realized the amplification of sound is advisable except in special instances in which it is contra-indicated. Generally amplification brings at least a portion of the speech signal within the normal acuity range allowing audition to form an integral part of the understanding and monitoring systems.

In order for audition to become an integral part of the receiving and monitoring system it must form a consistent part of the communicative signal. It is not enough to give the child experience with audition during speech instruction periods alone. In fact, isolated experience with speech-hearing probably prevents the establishment of any one system of control. Rather it demands that the organism shift to different feed-back and receptive systems as audition is included or removed from the circuit. Under such circumstances there is the likelihood that neither method can achieve its full potential. This concept then, suggests that when amplification is indicated, its use throughout the day should be gradually adopted.

The accomplishment of the most adequate possible means of speech reception and monitoring is a fundamental criterion of speech instruction. The effective reception of speech (good ability to comprehend spoken language) is important to the growth of the vocabulary, the formulation of ideas and their expression in well-structured sentences. The greater accessibility of speech when the auditory cues are available enhances and accelerates total language development. The establishment and consistent use of a sensitive responsive mechanism for both speech reception and speech monitoring can be achieved through daily speech experiences. The speech instructor provides a graded series of experiences designed for simultaneous growth in various linguistic skills. Thus speech training involves the ability to comprehend speech and the acquisition of new vocabulary, particularly the more abstract concepts. It engages the child in various kinds of expressive skills; those designed to facilitate the use of coherent sentence patterns and those planned to achieve good acoustic results. It is planned further to develop an efficient monitoring system so that control of speech can become independent of the teacher's guidance.

Thus speech improvement for the hearing impaired evolves from growth in general communicative efficiency. Improved in the sensitivity and the fidelity of the self-speech and distance speech receiving mechanism is reflected in the more normal voice quality, articulation and inflectional patterns.

INFECTIOUS MONONUCLEOSIS

Medical Staff Conference

J. G. MATEER, M.D., Physician-in-Chief

Panel

ROBERT E. BIRK, M.D.*
EDWARD F. WILT, M.D.**
WARREN B. MASON, M.D.***
GERARD A. WEIGEL, M.D.***

Dr. Birk: This morning we are going to discuss one of the most common infectious diseases of the adolescent and young adult group, namely infectious mononucleosis. That this disease is becoming increasingly more common, or rather recognized, is noted by Farnsworth and Thorndike[1] in a recent article on student health. They state that at Harvard, in the academic year 1954-1955, there were 76 cases of infectious mononucleosis, 43 cases of viral hepatitis, and 11 cases of viral pneumonia in a student population of 10,300. Dr. Wilt will present the general features of this disease.

Dr. Wilt: This morning I would like to present some of the historical background and clinical features of infectious mononucleosis. One of the earliest descriptions of this disease was recorded in 1889 by Emil Pfeiffer,[2] who described a febrile illness in children characterized by generalized lymphadenopathy and splenomegaly. He called this condition glandular fever, and was careful in his description to differentiate its benign, self-limited course from the more fulminating progress of the acute leukemias. Nevertheless, in the years following his description this disease was frequently confused with the various forms of leukemia.

In 1920, Sprunt and Evans[3] described the characteristic peripheral blood picture of infectious mononucleosis, emphasizing particularly the increased number of mononuclear cells. They also coined the name "infectious mononucleosis".

In 1923, Downey and McKinlay[4] published their classical morphologic description of the white blood cells, differentiating particularly the appearance of the lymphocytes in this disease and in acute lymphocytic leukemia. However, the modern era in the diagnosis of infectious mononucleosis may be said to date from 1932 when Paul and Bunnell,[5] at the Yale School of Medicine, reported an increased amount of non-specific sheep cell agglutinens in the blood of patients with infectious mononucleosis. With this handy diagnostic tool, and the refinements of Davidsohn and others[6] differential adsorption procedure, the clinician was able to make the diagnosis of infectious mononucleosis in many cases that had previously been obscure. During the years subsequent to the introduction of this technique case reports filled the medical literature, indicating that this was truly a cosmopolitan disease found in all parts of the world. In all series, however, the highest incidence of the disease was reported in the age group 10 to 35 years.

This is an edited report of a current staff conference of the Department of Medicine of the Henry Ford Hospital.

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Infectious Mononucleosis

The etiology of infectious mononucleosis remains unknown. It is thought to be due to a specific viral agent. Nevertheless, this agent has never been isolated or identified, and, while the disease picture has been produced in monkeys by the injection of infected lymph node material, the results in human volunteers have never been so clear cut.

SHEEP CELL AGGLUTINATIONS

Type	Serum	Adsorbed by Guinea Pig Kidney	Adsorbed by Beef Erythrocytes
I	Serum Sickness	+	+
II	Normal	+	0
III	Infectious Mononucleosis	0	+

Table I: Illustrating the differential adsorption useful in differential diagnosis.

In Table I, I have listed the three types of non-specific sheep cell agglutinens. Type I, found in patients with serum sickness, viral hepatitis, and occasionally in the presence of leukemia, has been found to be adsorbed on both guinea pig kidney and beef erythrocytes. Type II, found in normal human serum is adsorbed on ginea pig kidney alone. Type III, found in patients with infectious mononucleosis, is adsorbed on beef erythrocytes only. This phenomenon of differential adsorption may be of great help to the clinician in making the diagnosis of infectious mononucleosis when the clinical picture is obscure.

With regard to the pathology encountered in this disease, at necropsy in the few cases that have terminated fatally, there has been found generalized lymphatic tissue hyperplasia with enlargement of the mediastinal and mesenteric lymph nodes. The liver and spleen are also enlarged. Microscopically, there is found a perivascular accumulation of normal and abnormal lymphocytes in every organ of the body including the lungs, heart and kidney.

There are many varied clinical pictures of infectious mononucleosis. The classical form of the disease is characterized by a low grade febrile course associated with anorexia, generalized muscular pain, headache and pharyngitis. On physical examination the patient may have a moderate amount of supra-ocular or periorbital edema and the pharynx may be brilliantly inflamed with a dull white exudate on the tonsillar pillars or tonsils. There is generalized but particularly posterior cervical lymphadenopathy, with the lymph nodes being discrete and not particularly tender. The spleen will be palpable in about one-third of all cases on initial examination and will be felt in about one-half of all cases sometime during the illness.

The cutaneous manifestations of this disease are quite varied, ranging from a very transient, erythematous, macular eruption on the chest and shoulders which dis-

appears in hours, to a widely disseminated, florid, morbilliform eruption which may persist for several days.

The abdominal form may present as an acute abdominal emergency, particularly as acute appendicitis. Presumably due to mesenteric lymphadenopathy, the patient may have nausea, vomiting, right lower quadrant pain, and abdominal rigidity. The diagnosis in these cases may best be made by the differential white blood count.

The neurologic manifestations also are quite varied, ranging from the mild nuchal rigidity which is a frequent presenting complaint to the overwhelming peripheral neuropathies with flaccid paralyses of the extremities, ascending bulbar paralyses with respiratory involvement, coma and death. There have been five reported fatalities from this type of central nervous system involvement.

The hematologic picture may be manifested clinically by evidences of a purpuric rash, ecchymoses and the presence of thrombocytopenia. It is in this particular form of the disease that ACTH and the adrenocortical steroids have recently been found valuable.

The prognosis in the uncomplicated case is uniformly good, with complete recovery without sequelae in from three to six weeks. The complications will be discussed in some detail later in the program, but I should like to bring to your attention the 16 reported fatalities of which 12 have been due to either splenic rupture or the complications of meningo-encephalitis.

The differential diagnosis, as you might well imagine, is lengthy, but in the presence of the characteristic findings and laboratory data I have described, the diagnosis should not be difficult.

Finally, a word regarding treatment. The therapy is entirely non-specific with the emphasis particularly on bed rest and symptomatic management. Bed rest should be enforced as long as the spleen is enlarged because of the danger of splenic rupture. The adrenocortical steroids have a very definite place in the management of these patients, particularly in the severely toxic individual with jaundice or thrombocytopenia. In these cases a very prompt clinical remission may be expected.

Dr. Birk: As Dr. Wilt has mentioned, this disease is still of unknown etiology, and therefore, everything that he has said and all that we will say from here on, may well be contested. This is true, of course, in any disease in which the etiology is undetermined. Any definite statements regarding diagnostic studies, results of specific therapy or prognosis of infectious mononucleosis must necessarily be made in a tentative way, as th non-specificity of the various diagnostic tests does not permit for definitive evaluation.

We have personally seen 17 cases of infectious mononucleosis in hospital personnel in the past year and fortunately, so far, have had no complications. However, there have been reported a great many complications of the disorder which Dr. Mason will now discuss.

Dr. Mason: The complications of infectious mononucleosis have been divided into eleven categories as shown in Table II, taken from an article by Dr. Jason N. Smith,[7] formerly of the Division of Gastroenterology. Actually not all these manifestations can be considered as complications, but rather, some are manifestations of a systemic

COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS

1. Neurologic — 64 cases
2. Splenic Rupture — 21 cases — 7 deaths
3. Hepatitis — nearly all — Jaundice 6.6% in one series
4. Hemolytic anemia — 16 cases
5. Thrombocytopenic purpura — 16 cases
6. Pulmonary — 2% in one series
7. Cardiac — 9 cases of pericarditis
8. Abdominal
9. Renal — hematuria 6% in one series
10. Eye — common — papilledema in 4 cases
11. Dermatologic — rash 8% in one series

Table II

A listing of complications modified from Smith's[7] article.

disease. Since infectious mononucleosis may involve all organs, symtoms involving other than the lymph nodes, liver and spleen may be the presenting complaint.

The first complication to be discussed is neurologic. The number of reports has been rapidly accelerating in recent years. Neurologic complications can be subdivided into six parts, the first of which is serous meningitis. It is manifested by headaches, stiff neck, and increased spinal fluid pressure. Actually this is quite common; however, only four acceptable cases are recorded. The second sub-division is meningitis which gives the same symptoms plus signs of meningeal irritation. Ten cases have been reported. The third sub-division is meningeal encephalitis which has all of the above symptoms plus lethargy, dizziness, staggering, aphagia, nystagmus, hemiplegia, convulsions and coma. The fourth sub-division is pure encephalitis of which 20 cases have been reported. The fifth sub-division is that of a Guillain-Barre like syndrome with weakness, flaccid paralysis and a high spinal fluid protein of which 18 cases have been reported plus the two cases reported from this institution. There have been four deaths of this type. The sixth sub-division is that of peripheral neuropathy. The diagnosis is quite difficult since neurological signs may be the presenting complaint. Often the diagnosis is made by accident after routine smear has been obtained.

The second major manifestation or complication is that of rupture of the spleen. Twenty-one cases of spontaneous rupture have been reported with seven deaths. There is an invasion of the fibrous structure of the splenic capsule with lymphocytes. Weakening of these structures results, and rupture may occur with minor trauma, even that of palpation. After rupture, when peritonitis begins, there may be a shift to the left of the white cells and the smear will appear more normal, thus making the diagnosis more difficult.

The third complication is that of hepatitis. It is now believed there is some involvement in nearly all cases. Jaundice has been reported to occur in 6.6 percent of one series. The damage is thought to be of the hepatocellular type, rather than obstructive.

The fourth complication is that of acute hemolytic anemia of which 16 cases have been reported. Lack of anemia was always considered a good differential point from leukemia. It has been suggested that the enlarged spleen forms autohemolysins. The Coombs' test has been found positive in four cases and negative in one. As the heterophile titre drops the hemolysis stops and splenectomy is not necessary, although it has been done in one instance. ACTH and cortisone are effective in this complication.

The fifth major manifestation is thrombocytopenic purpura, 16 cases of which have been reported. Mild bleeding phenomena, such as epistaxis, have been commonly reported but true thrombocytopenia occurs explosively at the height of the disease. These people always recover with transfusion. Only recently it has been reported that ACTH and cortisone are effective in treating this particular complication.

The sixth major manifestation is that of pulmonary complications. Pneumonia has been commonly reported and pleural effusion has been noted in one case. The x-ray picture is said to be that of viral pneumonia while the cough is said to simulate pertussis.

The seventh major manifestation is that of cardiac complications. These are usually subclincal and benign; that is, there are non-specific electrocardiographic changes. However, nine cases of pericarditis with chest pain, friction rub and elevated RST segment with inverted T waves have been reported with no deaths.

The eighth complication or manifestation is that of abdominal involvement. This has been mentioned by Dr. Wilt and these represent manifestations of the enlarged mesenteric nodes.

The ninth manifestation is that of the renal complications. Red and white blood cells have commonly been reported, but only rarely do albumin or casts appear in the urine. In one epidemic six per cent of the cases presented as hematuria. There is no known association of these transient changes with coexisting chronic renal disease.

The tenth group is comprised of complications occurring in the eye. Oculomotor palsies are the most frequently reported. Papilledema has been reported both with and without neurologic complications. There is frequently a dry granular conjunctivitis, often unilateral and strangely enough, most often occurring on the left.

The eleventh manifestation is that involving the skin. Rashes have been reported in as high as seven percent in one series of 210 sporadic cases. The rash may be of any type, and has been described as macular, maculo-papular, urticarial, hemorrhagic, erythemamultiforme-like, and morbilliform.

Dr. Birk: Dr. Quinn has probably seen as many cases of infectious mononucleosis in this hospital as any other person, with the possible exception of Dr. Monto and his group. He has also reported three major neurological complications. Dr. Quinn, I wonder if you would comment on the neurological complications?

Dr. Quinn: (Physician-in-Charge, Division of Infectious Disease):

In the Henry Ford Hospital 239 cases of infectious mononucleosis were indexed in the years between 1925 and 1953. Nervous system involvement was noted in only five cases; in two it took the form of an aseptic meningitis. In the other three cases an acute polyradiculoneuritis of the Guillain-Barre type developed. These were reported by Drs. Raftery, Schumacher, Grain and myself in 1954.[8]

In a review of the literature reported in 1950, Bernstein and Wolff[9] estimated the incidence of central nervous system complications in infectious mononucleosis as probably less then 1 percent.

The types of neurologic manifestations which have been described fall into four main categories:

a. Lymphocytic or serous meningitis
b. Meningoencephalomyelitis
c. Acute polyradiculoneuritis
d. Peripheral neuritis

The two cases of aseptic meningitis were both diagnosed in the 1952 poliomyelitis epidemic when all cases with "non-paralytic poliomyelitis" were examined by blood smear and heterophile agglutinations. These patients presented minimal symptoms and signs suggestive of infectious mononucleosis.

The 3 cases reported as the Guillain-Barre syndrome were all males, and their ages were 24, 16 and 50. In one case both the heterophile agglutination and blood smear were considered diagnostic, while in the other two cases only one of these two tests was positive, the typical blood picture in one and the positive heterophile reaction in the other. All three patients demonstrated typical neurologic findings of acute polyradiculoneuritis and had increased spinal fluid protein and an absence of pleocytosis in the spinal fluid.

Two of these patients were moderately ill and one was severely ill requiring a period of ten days in the tank respirator. When last seen for follow-up, all exhibited some residual muscle weakness and disability.

We also reviewed the Henry Ford Hospital records for the indexed cases of Guillain-Barre syndrome and encountered 34 cases in the ten year period from 1943 to 1952. In four cases the illness was preceded by a "cold," three cases followed a sore throat, and in two there was a history of "flu." One case followed an acute gastroenteritis. The three cases referred to above were associated with infectious mononucleosis, and the remaining 22 cases presented no history of preceding illness.

Dr. Birk: Dr. Abraham, would you care to comment on the hematological complications and your thoughts concerning what Dr. Mason had to say about them?

Dr. Abraham: (Associate Physician, Division of Hematology):

With regard to the hematologic complications, they are often not the most striking and consequently we see perhaps less than 50 percent of the total number of cases in the hospital. Nevertheless, they justify some brief discussion.

Significant anemia is not a frequent complication, and its occurrence usually casts

some doubt on the diagnosis. However, a few cases of infectious mononucleosis have been accompanied by hemolytic anemia.

Neutropenia may occasionally be so pronounced as to suggest agranulocytosis.

Bleeding phenomena, particularly epistaxis, hematuria, or petechiae on the skin are not unusual. Rarely, fullblown thrombocytopenic purpura is observed.

Rupture of an enlarged spleen is a striking but unusual complication. However, it does indicate the need for some restraint in repeated palpation of that organ.

In a different sense, confusion with leukemia is indeed a complication for the attending physician.

Fortunately, serious hematologic complications are rare and the prognosis in general is good from our standpoint.

Dr. Birk: One of the most confusing of the differential diagnostic features to be clarified is that of hepatitis in infectious mononucleosis versus infectious hepatitis. Dr. Mason has already touched upon this and Dr. Weigel will now discuss it more thoroughly.

Dr. Weigel: The hepatitis that is associated with infectious mononucleosis is still subject to both clinical and pathological difference of opinion. Jaundice was first reported in infectious mononucleosis by Mackey[10] in 1926, and it was originally considered that the basic responsible factor was lymph node enlargement impinging upon the common duct with obstruction. The work of Bang and Wanscher[11] then suggested that the liver was actually involved with a pathological process of a parenchymatous nature. They felt that this was pathologically indistinguishable from infectious viral hepatitis. Recently, a number of workers have agreed that while some degree of hepatitis exists in practically all cases of infectious mononucleosis, both the pathology and the therapeutic implications are different from those of true viral hepatitis.

There is general agreement concerning the clinical manifestations of the liver involvement in infectious mononucleosis and these general observations may be made. About 15 to 25 percent show hepatomegaly at some time during the course of their disease and about five percent are jaundiced. The jaundice usually appears during the second week of illness, after the patient has sought medical attention earlier because of fever, malaise, sore throat or some other symptom frequently associated with the process, as opposed to the usual patient with hepatitis who is jaundiced when first seen or within a very few days thereafter. The jaundice of infectious mononucleosis is seldom marked and usually clears in two or three days. However, cases have been reported with jaundice persisting for eight weeks. The absence of pain, the presence of fever, lymphadenopathy and splenomegaly tend to favor the diagnosis of infectious mononucleosis, but can occur in hepatitis. It is to be noted that the presence of a sore throat is the most helpful feature clinically differentiating infectious mononucleosis from infectious hepatitis.

Liver function studies are somewhat variable but it is agreed that the cephalin-cholesterol flocculation test is positive in at least 95 percent of cases. The bromsulphalein and thymol turbidity tests are very frequently positive and as much so as in hepatitis. An elevated alkaline phosphatase suggests that there is some degree of

obstructive feature to the hepatitis and determinations considerably above the dividing line of 10 Bodansky units are not infrequent. It is generally considered that leukocytoid lymphocytes can occur with infectious hepatitis though they definitely tend to be fewer in number. A significant heterophile determination is the salient feature in distinguishing the two entities.

Pathologically, the findings by liver punch biopsy are essentially the same in jaundiced and non-jaundiced patients, and for practical purposes are present in every case of infectious mononucleosis. Hepatitis is a regularly occurring feature of the disease and not to be considered a complication. This is not surprising in view of the fact that the hepatic mesenchymal cells may be lymphocyte precursors and the etiological agent of infectious mononucleosis, whatever it may be, seems to stimulate lymphocytic production and development. The pathological features of infectious mononucleosis are the presence of large numbers of mononuclear cells in the portal areas with foci throughout the lobules and within the sinuses. About half the cases show eosinophils in the periportal exudate but neutrophils and plasma cells are absent.

The pathological features of infectious mononucleosis distinguishing it from hepatitis are on the negative side, in that there is very minimal hepatocellular damage, occurring only in areas where foci of lymphocytes within the lobules encroach mechanically upon the surrounding liver cells. Eosinophilic degeneration, which has been earmarked as characteristic of hepatitis does not occur, and there is no distortion of the hepatic architecture. In general it may be said that the hepatitis of infectious mononucleosis tends to be much more a mesenchymal and much less a parenchymal type process than is infectious hepatitis.

These pathological features have clinical application in the follow-up care of the hepatitis of infectious mononucleosis, which in general tends to be mild. There has been one case reported of cirrhosis following mononucleosis, but on closer perusal one questions whether or not this was merely a coincidental occurrence. There have been two cases of fatal liver involvement reported; but again, when one considers the vast number of cases of infectious hepatitis and the extreme frequency of liver involvement, one hesitates to attribute this liver damage solely to the infectious mononucleosis.

There would, in general, appear to be pathological support of the concept that one need not be too severe in the restriction of activity of patients who have laboratory evidence of hepatitis in infectious mononucleosis. If the patient is afebrile and otherwise asymptomatic even when jaundice is still present, it would seem logical to begin gradual ambulation. Long-term follow-ups by Hoagland[12,13] tend to support this. He has had no complications using a program allowing ambulation when fever and clinical symptoms have abated.

Dr. Birk: Dr. Haubrich would you care to comment on Dr. Weigel's presentation?

Dr. Haubrich: (Associate Physician, Division of Gastroenterology):

In commenting on a truly generalized disease, those of us representing the various subspecialties run the risk of casting ourselves in the roles of the five fabled blind men sent to examine the elephant. To him who felt the ear, the elephant was like a fan; the tail was likened to a rope, the leg to a tree, and so on. Infectious mononucleosis is a *generalized* disease, and it is not surprising that its manifestations are varied.

Using "hepatitis" in the generic sense, we are reminded that inflammation within the liver may be induced by any of at least 25 distinct pathogenic organisms; viral, bacterial, spirochetal, and protozoan. Conversely, the virus of infectious hepatitis may induce disease in extra-hepatic systems, e.g., myocarditis and atypical lymphocytosis.

There are three aspects of the relationship between infectious mononucleosis and the liver which deserve emphasis:

(a) At least 80 per cent of patients with infectious mononucleosis will exhibit aberrations in so-called liver function tests, particularly in the flocculation and turbidity tests which depend upon poorly defined changes in the serum protein content and only indirectly reflect liver function. Hepatomegaly is observed in about 15 per cent and frank jaundice in about 5 to 10 per cent of patients. I am sure that the incidence of *actual* liver involvement lies somewhere between these extreme figures.

(b) Regarding the histologic distinction within the liver between infectious mononucleosis and infectious hepatitis, we may look upon the former as primarily a reticuloendotheliosis with attendant inflammation and upon the latter as a direct injury to the parenchyma itself. Granted that it is seldom such a black-and-white situation to the pathologist examining a liver biopsy, nevertheless, I offer this as a useful concept.

(c) Finally, as Dr. Weigel has stated, the hepatitis component of infectious mononucleosis is almost invariably short-lived and benign. I am not aware of a single *bona fide* instance of lasting liver damage which can be rightfully attributed to a single attack of infectious mononucleosis.

Dr. Birk: In Table III, you will note listed six representative cases of the 17 that we personally have seen in the past year. These six cases were selected because they represent features of the disease which are particularly striking. I wish to point out especially the frequency of fatigue as a presenting symptom, either alone or in combination with one of the other symptoms of this disorder. It is safe to say that all patients with infectious mononucleosis complain of fatigue to a greater or lesser degree, and that it is the predominant factor in the morbidity.

The first three cases are essentially similar in that they are white, female, 19 year old student nurses. The first case is significant in that the heterophile titre is so high, that is, 1:245,376. There were also a high percentage of leukocytoid lymphocytes and very positive liver flocculation studies. This young lady was toxic for some time, and her symptoms of severe fatigue, anorexia, and malaise persisted not only for a total of 46 days, but were so pronounced that she was unable to return even to classes, and consequently was forced to lose a full year in her training. This loss of time certainly must add to the total morbidity as most of these people are in the student age group.

It is interesting to note that the second patient also had a high heterophile titre, as our titres go, with a high percentage of leukocytoid lymphocytes and that while both had very positive liver flocculation tests, neither had jaundice.

The third case is interesting in that only cervical adenopathy was present and that the degree of morbidity was somewhat less. The first three cases alone would seem to indicate that the degree of toxicity is related to the elevation of the heterophile titre. The fallacy of this is shown by the last three cases, particularly the fourth.

REPRESENTATIVE CASES OF INFECTIOUS MONONUCLEOSIS

Number	Sex	Age	Presenting Symptom	Days of Symptoms	Fever	Nodes	Spleen	Liver
1.	F	19	Fatigue	46	+	G	+	+
2.	F	19	Sore Throat	9	+	G	+	+
3.	F	19	Sore Throat	7	O	Cerv	O	O
4.	F	18	Nausea, Fatigue	13	+	G	+	+
5.	M	16	Fever, Headache Sore Throat	25	+	G	+	+
6.	F	26	Fatigue, Hematuria	10	+	G	O	O

Number	Sex	Age	Other Signs	Highest Heterophile	Highest % L. L.	Highest C. C.	Liver T. T.	Floc c T. F.
1.	F	19	Strep Exudate	1:245,376	73	4+	12u	4+
2.	F	19	Strep Exudate	1:7168	67	3+	7u	4+
3.	F	19	Strep Exudate	1:896	30	3+	1u	+
4.	F	18	Rash	neg.	19	3+	5u	3+
5.	M	16	Exudate Eye edema	1:1792	68	3+	3u	+
6.	F	26	Eye edema	1:3584	40	3+	5u	3+

Table 3: Six cases of the seventeen seen in past year, representing major clinical features.

This girl had 13 days of toxicity with all the other features of severe infectious mononucleosis but with negative heterophile titres and only a few leukocytoid lymphocytes on repeated examinations.

The first three cases also illustrate another important point, that is the common association of beta-hemolytic streptococcic pharyngitis and infectious mononucleosis. This association may exist with or without the typical white, membranous pharyngeal exudate of infectious mononucleosis. I would like to emphasize this point and urge that every patient with infectious mononucleosis have a throat culture. The hemolytic streptococcus, if present, should be treated adequately with penicillin.

Case three illustrates also the absence of a palpable spleen which, as previously noted, is not infrequent. Another point deserving emphasis is that once the spleen is found it would be then best left alone. Many patients have been seen initially in the clinic and a non-tender spleen and liver palpated. On subsequent examination the next day, after repeated examinations during the admission procedure, both were extremely tender, with much discomfort to the patient and increased risk of trauma.

Case number four had a classical picture of infectious mononucleosis plus a morbilliform rash for three days, despite a negative heterophile and few leukocytoid lymphocytes. Wintrobe[14] states that the heterophile titre is positive in only 60 percent to 92 percent of the series he has studied and that a titre of 1:64 is significant. It is interesting to note that Leibowitz,[15] who admits that he was probably the only exponent of excluding the diagnosis unless the heterophile was positive, recently reported three cases of infectious mononucleosis with a negative heterophile titre. He relates this to the possibility of two different but related viruses, a "non-reactive" patient, or of a test incorrectly done.

Case five illustrates the disease in a young boy, who was quite toxic for four or five days with fever, headache and sore throat before being admitted. He continued to have fever and marked malaise for another five days and, because of the increasing toxicity and high fever, he was treated with steroids. He received hydrocortisone in decreasing doses over a period of six days. It is interesting to note that his symptoms and fever completely disappeared in 12 hours and he made a very rapid and uneventful recovery.

Case five and six both illustrate one of the frequent signs of this disease which is easily missed unless looked for, that is periorbital edema. Both had marked periorbital edema, to the extent that case six was mistaken initially for primary renal disease. This patient had a history of acute glomerulonephritis at the age of six and was seen complaining of periorbital edema and fatigue for approximately a week. Initial urinalysis revealed microscopic hematuria, slight albuminuria and a few casts. Two days later, while under observation, she developed generalized adenopathy and the diagnosis became evident. The hematuria as well as the casts and albumin were present for the first two days and then disappeared entirely.

One last point is illustrated by a 24 year old white female who, in November of 1956, had 10 days of marked anorexia, fatigue, sore neck and malaise. She did not consult a physician at that time. She was seen approximately three months later complaining of fatigue, anorexia and stiff neck. Examination revealed generalized adenopathy and a palpable spleen and liver. She stated she had not felt "right" for three months. Laboratory studies were entirely negative, and she made an uneventful

recovery after one week of bed rest and limited activity for a short time. I feel that she had a relapse of infectious mononucleosis which originated three months before, or that the "post-viral asthenia" was this long drawn out. Wintrobe[14] states that recrudescences are quite common and may occur in about six percent. A recent article by Koyl[16] describes a new disorder, "infectious reticuloendotheliosis", which is characterized by long standing fatigue and irritability and may well represent long standing post infectious mononucleosis asthenia.

As far as treatment is concerned, I must disagree wholeheartedly with the statement that bed rest is unnecessary. Treatment of the associated hepatitis by rest is not indicated, but total rest while toxicity persists does seem to promote quicker recovery and does seem to prevent further relapse. After symptoms disappear, limited activity is indicated as this also seems to reduce the total period of morbidity.

No special diet, other than a good general one is indicated, as Dr. Weigel has stated.

The use of penicillin in those patients with an associated beta hemolytic streptococcal infection is imperative. This is probably the most frequently overlooked intercurrant infection with infectious mononucleosis and needs treatment to prevent prolonged toxicity during the acute episode or further disability from the streptococcus at a later date.

As to the use of steroids, aside from their use in the severe complications where it is of unquestionable value, if the patient does not become afebrile and relatively asymptomatic after five days, the use of steroids in moderate dosage for about six days seem to promote symptomatic recovery and may prevent longstanding morbidity.

We now have some time for discussion.

Dr. Frank R. Menagh: (Consultant, Division of Dermatology): Are antibiotics routinely used in treatment?

Dr. Birk: Antibiotic therapy is not indicated unless it is for an associated infection, especially with the beta-hemolytic streptococcus, in which case adequate penicillin is indicated. If the patient is penicillin sensitive, other antibiotics, usually the tetracyclines, are used.

Dr. Mateer: Do you think the use of steroids in the non-complicated case causes a reduction in the total morbidity?

Dr. Birk: I do not feel that steroids actually shorten the course of the disease in any way except to reduce the severity of the symptoms. This may, however, promote faster recovery by increasing the appetite and so forth. Dr. Quinn, would you comment on that?

Dr. Quinn: We are not now able to determine whether a specific treatment is of any value in this disease because of the lack of properly controlled studies. We should set up such a study and attempt to evaluate the effectiveness of steroid therapy.

Dr. C. E. Rupe: (Physician-in-Charge, Medical Clinic #4): How long can the latent period be before the appearance of leukocytoid lymphocytes in the smear?

Dr. Birk: One recent case had a 21 day period from the onset of fatigue and anorexia to the clinical picture. She, however, had negative heterophile titres and only 13 percent leukocytoid lymphocytes at that time. There may have been a time in this 21 day period in which she had more positive findings which were not detected.

Dr. Weigel: Ninety-five percent of the cases show a positive heterophile titre, if it is going to become positive, in the first determination, and the titre most frequently becomes positive within the first two weeks.

Dr. Birk: The practice of drawing an initial heterophile determination in a patient with the clinical picture of infectious mononucleosis and discarding the diagnosis because of a negative result should be avoided however.

Dr. Robert Nixon: (Associate Physician, Division of General Medicine): I should like emphasized two points in connection with certain of the comments that have been made. First of all, patients with infectious mononucleosis may reveal initially only a mild leukocytosis with a neutrophilia without changes in lympocytes for sometime up to a week before atypical lymphocytes make their appearance. In addition, there may not uncommonly be a premonitory eosinophilia again antedating the apperance of classical changes in the lymphocytes.

Insofar as the differentiation of the hepatitis which may occur in infectious mononucleosis from that of ordinary viral hepatitis, the following may be stated: in most instances, the peripheral smear reveals a much more marked degree of lymphocytosis and characteristically the finding of all types of atypical or leukocytoid lymphocytes in infectious mononucleosis with hepatitis, whereas, in infectious hepatitis one rarely sees more than a few, i.e., 5 percent to 20 percent atypical lymphocytes, without the marked variation in types referred to in infectious mononucleosis. Hence, in most instances, the degree and character of the atypical lymphocytes of infectious mononucleosis hepatitis is fairly easily differentiated from ordinary viral hepatitis. Of course, the other clinical and serological features will also make this differentiation clear.

Dr. Birk: Thank you. Our hour is up.

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THE RESPONSIVENESS OF THE RESPIRATORY CENTERS IN CARDIACS WITH MITRAL VALVULAR DISEASE

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In testing the responsiveness of any neurological motor center the increase in the state of activation by a given increase of its specific stimulus has to be determined. For the respiratory centers, the gas tension of carbon dioxide in the arterial blood ($PaCO_2$) is considered to be the predominant stimulus. The best indication of the state of activation appears to be the total ventilatory volume per unit time.[17] A given increase of the arterial CO_2 pressure should lead to a specific increase in total ventilation, according to the following stimulus — response relationship: $\frac{\triangle \dot{V}}{\triangle PaCO_2}$.

If ventilation is measured in liters per minute and gas tension in millimeters of mercury, the thus obtained value will be the increase of ventilation in liters per minute effected by 1 millimeter of mercury increase in CO_2 tension. Henceforth, we will refer to this ratio as the quotient of responsiveness (QR).

The increase of the arterial CO_2 tension can be effected stepwise by inhalation of various concentrations of CO_2, or by the addition of artificial respiratory dead space. For our purpose, the most satisfying method seems to be a gradual increase in CO_2, brought about by a closed system of ventilation using no device for CO_2 removal. Such a method, somewhat modified from the one described by Julich[6] has been used in this experiment.

In this procedure, the subject inhales from an 80-100 liter reservoir of oxygen, to which the exhaled gas is returned (Fig. 1). The CO_2 of the circulating gas, therefore, gradually increases. Ventilation is measured by readings from a gasometer. Oxygen

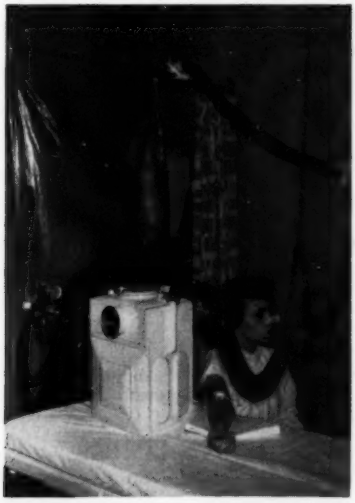

Fig. 1. Apparatus for testing respiratory response to variation in CO_2 concentration.

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is used instead of room air to ensure full arterial oxygen saturation throughout the test, therefore eliminating possible activation of the chemoreceptors for lack of oxygen. It also has the advantage of making the experiment better tolerated especially by cardiac patients for whom the desired levels of hyperventilation constitute considerable exertion. Through an indwelling Cournand needle in the brachial artery blood specimens are obtained in heparinized syringes at specific stages of the test. These are examined for O_2 and CO_2 content with the Van Slyke apparatus and technique, and for pH using a Cambridge electron-ray meter. Before the actual rebreathing study begins, the subjects breathe 100% oxygen usually for 25-30 minutes through the apparatus as described, until a steady state of ventilation and arterial CO_2 tension is reached.[7,16] The first sample of blood is drawn at this point. Subsequent samples are drawn at three levels of CO_2 increase in the inspired gas, as determined by concurrent ventilation measurements. Minute volume is calculated from three minute gasometer readings of the inspiratory volume immediately preceding the collection of each blood sample.

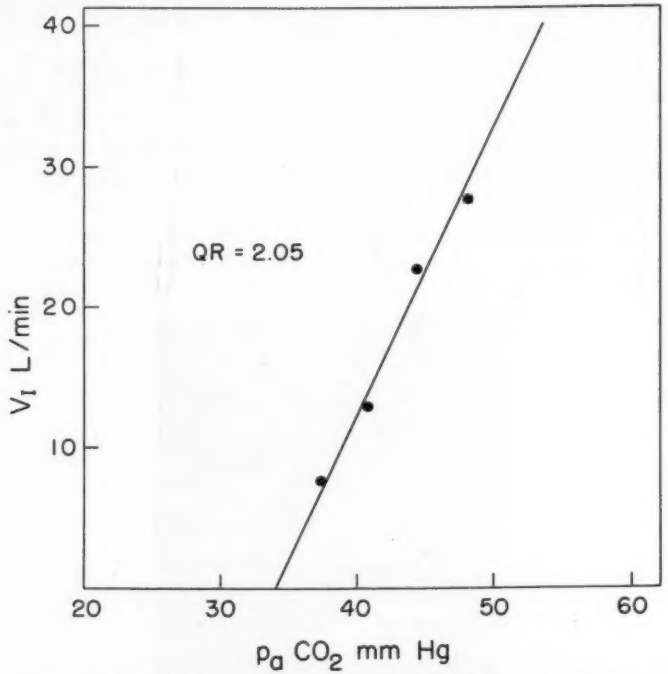

Fig. 2. Curve of respiratory minute volume from a normal person exposed to rising concentration of CO_2.

Fig. 2 represents the curve obtained by this method from a normal, 30 year old male. The relationship between $\dot{V}$ and $PaCO_2$ is a linear one.[1,5] This has been confirmed by our results. The time required to produce a minute volume of about three times the resting level (25-30 L/min.), was generally between 40 and 60 minutes. There is, of course, at no point a complete "steady state". Considering the slowness of CO_2 accumulation and the strictly comparative value of the obtained results, this

does not seem to be necessary. Gas samples obtained in eight tests at the end of the experiment from the inspiratory side of the circuit were analyzed using the Scholander technique. The CO_2 content was between 4.91% and 7.54%.

It is apparent that an increase of the CO_2 tension by 1 millimeter will produce a different respiratory response depending on body size and build. The obtained QR was therefore calculated per square meter body surface.

One of the main purposes of this study has been to establish a satisfactory and simple method. The most extensive knowledge of respiratory responsiveness using comparative methods has previously been acquired in pulmonary emphysema. Relatively little is known of respiratory responsiveness in cardiac patients. We have, therefore, studied a group of cardiac patients, mostly with valvular lesions amenable to surgery. Technically satisfactory results have been obtained thus far in 30 tests on 26 persons. Eight patients had rheumatic heart disease with either pure or predominant mitral stenosis (group I). These were subdivided as follows:

(a) two patients with less than 10 years duration since the active phase of rheumatic fever, functional classification I and II.

(b) six patients with more than 10 years duration since the active phase of rheumatic fever; their functional classification was II and III.

Fig. 3 represents the curve obtained from a 51 year old female with inactive rheumatic heart disease and a predominantly stenotic mitral lesion, who was known to have specific cardiac symptoms since the age of 31. The next group (group II)

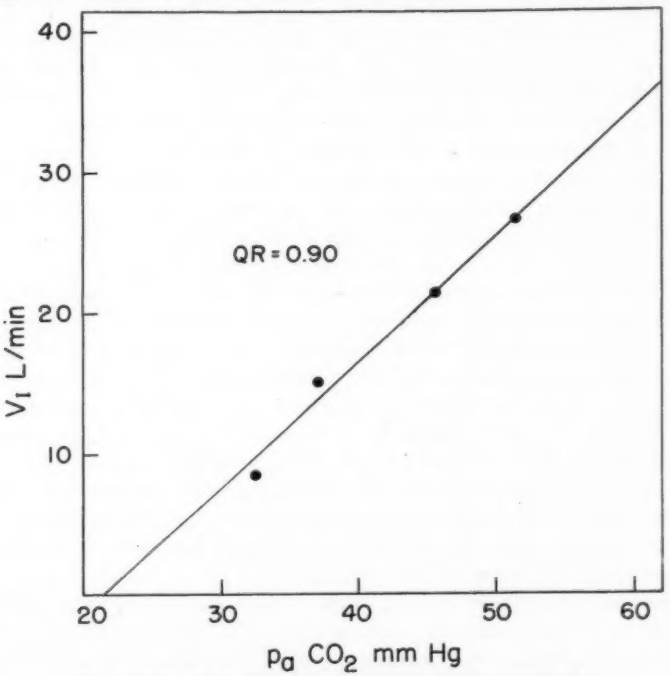

Fig. 3. Curve of respiratory minute volume from a patient with inactive mitral stenosis exposed to rising CO_2.

includes four patients suffering from rheumatic heart disease with combined mitral and aortic lesions, also belonging to the II and III functional classifications. The specific diagnosis in these two groups was made by clinical, X-ray and EKG findings, with the addition of left heart catheterization in some. A third group includes three patients with congenital heart disease, diagnosed as patent ductus arteriosus in two and interventricular septal defect in the third, confirmed by right heart catheterization. Functional classification in this group ranged from I to III. None of the patients was cyanotic. Two had marked pulmonary hypertension, while one had a normal pulmonary artery pressure.

The results which are essential for this study are averaged for the four groups and shown in Table I. Three tests on three patients with the diagnoses of idiopathic pulmonary fibrosis, arteriosclerotic heart disease with congestive heart failure and rheumatic mitral stenosis, complicated by severe anemia are not included. Seven patients in group I, all in group II and one in group III underwent corrective cardiac surgery. Only three patients have been studied post-operatively to date.

Thus far, we have been unable to demonstrate any significant deviation from the normal level in the groups with combined valvular lesions and congenital lesions. This might be due to the statistically insignificant number of patients examined. The average of a QR/m^2 of O.65 in patients with mitral lesions as compared to 1.03 in normals suggests a reduced responsiveness in the first group. These changes appear to develop late in the course of rheumatic heart disease.

DISCUSSION

The ventilatory response to the CO_2 stimulus has been studied by several authors,[1-14] with different methods of artifical CO_2 accumulation. Chronic diffuse pulmonary emphysema has been the main pathological entity investigated and shown to be associated with a decrease of the responsiveness of the respiratory centers. It has been questioned if this represents a true reduction in the central responsiveness.[2] The degree of activation of the centers can only be estimated indirectly through its effect upon the respiratory apparatus, which indeed, is grossly altered in pulmonary emphysema. While there is no doubt about the role of the mechanics of breathing in bringing about these changes, a true central alteration appears to be proven by several facts. The same decrease in responsiveness of the respiratory centers that occurs in pulmonary emphysema has been produced artificially in normal individuals by long term exposure to a CO_2 enriched atmosphere, without changes in the mechanics of breathing.[12] Conversely, respiratory responsiveness in two emphysematous patients seems to have been restored towards normal by long term treatment with artificial respiration, poducing marked diminution of the chronic CO_2 accumulation.[15] These findings, plus the fact that normal central responsiveness has been found in emphysematous patients without chronic CO_2 accumulation,[1] indicate the important role of chronic CO_2 overload in these central changes. Furthermore, responsiveness of the respiratory centers in normal subjects and emphysematous patients can be significantly altered by several drugs, such as morphine,[5] and salicylates, [13,14] and mecodin.[10]

Cyanotic congenital heart disease, chronic metabolic acidosis and alkalosis have been studied to a lesser extent in a comparable way. In these three conditions only chronic metabolic alkalosis was associated with a diminished responsiveness of the respiratory centers, which stresses again the role of CO_2 accumulation as the main factor.[1]

TABLE I

	No. of Pts.	Average Age	Average Resting Ventilation Under 100% 0_2 per m^2 Body Surface	Arterial blood studies						
				Average Resting Arterial CO_2 Tension		Average Quotient of Responsiveness		Average pH	Average Oxygen Saturation	
				PCO_2					SO_2	
			Vi L/min./m^2	Under Room Air	Under 100% O_2	QR	QR/m^2	pH	Under Room Air	Under 100% O_2
GROUP I										
Rheumatic Heart Disease Pure Mitral Lesions										
Less than 10 yrs. duration since rheumatic fever	2	20	5.36	34.6	35.0	1.93	1.24	7.40	96.6	100
More than 10 yrs. duration since rheumatic fever	6	45	5.06	36.9	36.5	1.03	0.65	7.42	95.5	100
GROUP II										
Rheumatic Heart Disease combined Mitral and Aortic Lesions	4	42	6.16	35.0	34.5	1.49	0.95	7.42	97.1	100
GROUP III										
Congenital Heart Disease	3	32	5.29	36.0	34.4	1.69	0.99	7.41	88.7	100
NORMALS	8	34	4.67	37.8	38.3	1.85	1.03	7.42	96.7	100

Julich[5,11] has studied cardiac patients with a rebreathing method similar to the one used by us. He found an increased responsiveness of the respiratory centers in the over-all group with valvular lesions. In subdividing these patients according to their specific cardiac lesion, he found the values in patients with selective mitral lesions to be low normal or even diminished. We became interested in this fact as a possibility of obtaining more insight into the mechanisms of dyspnea in cardiacs with mitral lesions, which up to this time have not been fully explained by ventilatory and circulatory studies. The method might also have a certain value in estimating an unknown factor of secondary pulmonary disease in such patients.

Our results confirm to a more than expected degree the diminished respiratory responsiveness in patients with mitral valvular disease. The characteristic hyperventilation with hypocapnia found in other types of cardiacs is reduced in these patients, while their respiratory response to CO_2 accumulation resembles the one encountered in pulmonary emphysema. As indicated by the PCO_2 and pH values, there is no evidence of CO_2 accumulation in these patients. If these findings can be substantiated with a larger number of tests, we have here a pathological entity where diminished responsiveness of the respiratory centers cannot be explained by chronic CO_2 accumulation. Post-operative reexamination will give us an idea as to the reversibility of these changes.

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OBSERVATIONS ON PROTRACTED CYSTIC DUCT OBSTRUCTION WITH HYDROPS

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Hydrops denotes a large gallbladder distended with fluid resembling water. The condition is dependent on 3 requisites: a) complete and unyielding obstruction of the cystic duct, usually by stone, b) the absence of infection, and c) a gallbladder wall capable of distention and retaining a degree of permeability with relation to circulating blood plasma.

In the modern era of emphasis on prompt surgical correction of biliary tract obstruction, such a set of conditions is seldom permitted to persist. A remarkable instance in which hydrops evidently existed for approximately 6 years is herewith recorded.

REPORT OF CASE

HFH Case No. 318237: A 38 year old white housewife complained of "a lump in my side". Eight years earlier she had been seen at this hospital because of upper abdominal distress compatible with biliary "colic". At cholecystography the gallbladder had failed to visualize. Surgical intervention was advised. In making this recommendation, the physician unfortunately used the term "exploratory laparotomy". Apparently this carried a connotation too indefinite and inconclusive for the patient. Thanking him for his efforts, she departed and did not return.

Two years later, while turning on her left side in bed, the patient herself palpated a firm, smooth, non-tender, globular mass in the right hypochondrium. Thereupon, she consulted her family doctor who (allegedly without examination) indicated the mass might be her kidney and suggested that she consult a urologist. The urologist, in turn, following normal pyleography, assured her there was no disease in the kidneys. Armed with this information, and because the mass was quite asymptomatic, the patient dismissed her concern. Nevertheless, each time she chose to do so, she could easily palpate the unchanging "lump". Curiously, there was no recurrence of colicky pain, and only recently had the patient been aware of a slight soreness below the right rib margin.

Physical examination of this slender woman readily disclosed a prominent, globular mass in the right hypochondrium. The mass was only slightly tender and followed a full excursion with each breath. Laboratory data, including urinalysis, hemogram, serum bilirubin and alkaline phosphatase, were unremarkable. Diagnostic biliary drainage yielded no specimen which could be identified as "B-bile"; the duodenal aspiration contained no cholesterin crystals or bilirubinate pigment. Despite a "double-dose" of Telopaque, the gallbladder was not visualized at cholecystography.

On this occasion the patient readily accepted the recommendation for cholecystectomy. At operation a large, turgid, distended gallbladder was encountered. In order to facilitate dissection prior to resection the surgeon was obliged to aspirate 200 ml. of faintly opalescent, colorless, serous fluid (Figure 1). In addition, the gallbladder

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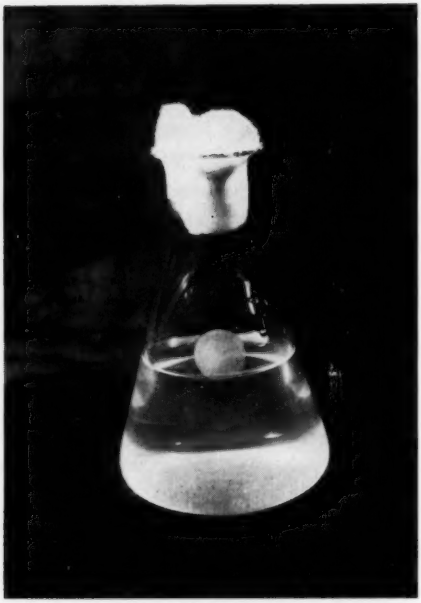

Figure 1. Serous, faintly opalescent fluid aspirated from the hydropic gallbladder; its contents are enumerated in Table I.

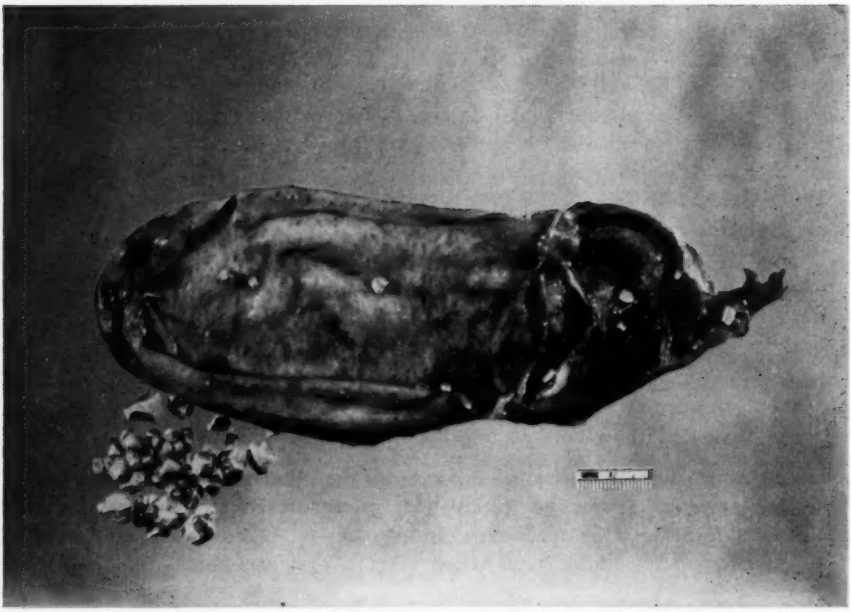

Figure 2. Thin walled, hydropic gallbladder opened along its longitudinal axis.

contained more than 50 small to medium-sized, faceted, mottled yellow and brown concrements. The cystic duct was of normal calibre; several stones were incarcerated within the cystic duct completely obstructing its lumen. The opened gallbladder measured 16.5 cm. in length, 9 cm. in circumference. Its wall was thin but fibrotic; the mucosal surface was smooth, dull, and grey (Figure 2).

The common bile duct and liver were grossly normal. An orthodox cholecystectomy was performed. The post-operative course was uneventful.

DISCUSSION

What happens in a gallbladder deprived of bile by protracted cystic duct obstruction? Given the 3 conditions previously enumerated, the answer hinges on the normal physiologic function of the gallbladder. Finally, this function may be modified by varying degrees of disease within the gallbladder wall.

In Table I a comparision is invited between the relative concentrations of various constituents making up the contents of the hydropic gallbladder herein described, "normal" gallbladder bile, and plasma. It seems reasonable to assume, if the gallbladder wall retains any permeability, that an equilibrium is established between the lumen of the gallbladder and blood plasma coursing through the bladder wall. That this equilibrium is not attained by simple diffusion is indicated by the discrepancies in concentrations listed in Table I.

Table I

	Contents of Hydropic Gall Bladder	"Normal" Gall Bladder Bile*	Plasma
Sodium (mEq/L)	144		145
Potassium (mEq/L)	4.9		4.8
Chloride (mEq/L)	162	16—19	105
Uric Acid (mg/100 ml)	17		3
Protein (Gm/100 ml)	0.012		7
Bile Salts (per cent)	0	2—9.7	0
Calcium (mg/100 ml)	5	25—28	10
Cholesterol (mg/100 ml)	0	160—540	180
pH	6.5	6.9—7.7	7.3

*From Sonderman, F. W., and Boerner, F. Normal Values in Clinical Medicine. Philadelphia, Saunders, 1949, p. 275.

As expected, sodium and potassium are isotonic. Chloride is relatively increased to make up the acid-base balance. Protein is apparently excluded from the gallbladder

lumen. Uric acid is unaccountably high. Bile salts are apparently absorbed. The concentrations of 2 common constituents of gallstones are of particular interest: cholesterol is absent from the hydropic fluid, and calcium is relatively low. The evidence from this one instance may suggest that the hydropic gallbladder is incapable of forming concrements of the usual type.

That the hydropic gallbladder may attain a gigantic size is substantiated in a report by Collinson[1] of a patient whose gallbladder became so large that abdominal paracentesis was performed (yielding 25 pints of fluid!) because of an erroneous diagnosis of ascites. The abdomen of this patient had gradually enlarged over 2 years; she eventually recovered after removal of the gallbladder. Terrier[2] cited the removal of over 42 pints of fluid from a gallbladder. Abdominal distention in this patient over 8 years had produced dyspnea. Evidence of hydrops existing for 12 years was reported by Doran.[3] The gallbladder of this patient contained one liter when resected. Waring[4] described a tremendously distended gallbladder, the lower part of which passed through the right femoral ring forming the contents of a hernial sac.

Why is cystic duct obstruction in some patients followed by hydrops while in others it is followed by the formation of thick, pasty, "milk-of-calcium" bile? In 1887 Birch and Spong[5] reported studies on 2 patients for whom cholecystostomies had been performed because of cystic duct obstruction and in whom the gallbladder mucosa was considered normal. In each 24 hours these gallbladders secreted approximately 20 ml. of clear, watery, slightly alkaline fluid which contained mucin, chlorides, carbonates, and phosphates, but no bile salts. On the other hand, secretion of calcium salts into the obstructed gallbladder may lead to precipitation of "milk-of-calcium" bile or calicification of the gallbladder wall.[6]

It has been our experience that the obstructed gallbladder containing "milk-of-calcium" bile is invariably a small, shruken gallbladder the wall of which is obviously and grossly diseased. In hydrops the wall is thin and the mucosa intact. It would appear, therefore, that the differential absorption and secretion by the gallbladder wall is a function of the inflammatory disease within that wall.

SUMMARY AND CONCLUSIONS

Protracted, complete cystic duct obstruction may result in relatively asymptomatic hydrops of the gallbladder. A case in which such obstruction was evident for 6 years is described. The sequence of differential absorption and secretion by the gallbladder wall following cystic duct obstruction seems to be determined by the extent of prior disease within that wall.

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ANXIETY AND ITS PHARMACOLOGIC CONTROL

ROBERT R. SCHOPBACH, M.D.*

"Peace be unto you." This has been an esteemed greeting from the earliest of times, and is indicative of man's great desire to obtain inner peace. However, anxiety, considered by some to be inherent in mankind, arises from time to time to disturb this state of inner peace. To reduce the frequency and severity of these disturbances man is constantly seeking additional calming measures. Reliance upon the protection of someone more powerful be that mother, spouse, or God, increases one's feeling of personal security. The measures in which we are more directly interested are those which serve to reduce the awareness of the disturbance and to reduce the physical responses to those stimuli. Frequently, new drugs are introduced as solving this problem only to fade into lesser positions later.

Probably the oldest and best liked sedative is alcohol. It is utilized much more than some realize to quiet jangled nerves. Unfortunately it is frequently habituating and has toxic side effects which are well known. The barbiturates are dispensed as if they were nearly harmless. However, here also habituation is common and close supervision and concern by the physician is necessary. Convulsions and other withdrawal reactions to barbiturates must be considered. Of the standard drugs, paraldehyde and chloral hydrate are the most desirable. Chloral hydrate is now available in a palatable liquid, 0.5 gm. capsules and tablets. Two recent additions to the long list of sedatives are methyl-prylon (Noludar) and glutethimide (Doriden) which are moderately potent and non-barbituric.

AMPHETAMINES AND RELATED COMPOUNDS

Sympathomimetic drugs and central nervous system stimulants are usually neglected as agents for reducing anxiety on the assumption that they would only increase tension. In certain depressive states the reverse is true as the agitation is secondary to the depression. To those unfamiliar with this response it is quite surprising to see a restless, agitated patient, when given amphetamines intravenously, begin to calm down within a few minutes, to smile, and to verbalize his pleasure with the subjective mood changes. This occurs only in those depressions having a strong affective component (reactive, so-called involutional, or manicdepressive, depressed). The neurotic depressives, where the depression is only one of a group of symptoms, do not obtain such relief but often experience an aggravation of their anxiety. This difference in reacting to the amphetamines can be utilized to help differentiate between these groups. For such a test 20 mgm. benzedrine (or its equivalent) is injected intravenously early in the morning when the affective depressions are usually worst. The response should be clear within 15-30 minutes. If the medication proves effective, it might thereafter be given orally upon arising and at noon. If given later in the day, it may impair sleep. If the depression is severe, the patient should, of course, be hospitalized and probably be treated with electro-shock therapy.

Some doctors hesitate to utilize these drugs in hypertensive individuals; however, I have never seen any marked elevations of blood pressures. Quite to the contrary, the blood pressure often decreases as the agitated depression is alleviated. Likewise

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appetite is improved rather than decreased as when amphetamines are taken by "normal" persons. This group of medications should be kept in mind and used as frequently as possible to reduce anxiety instead of barbiturates which sedate and may aggravate depressions.

AZACYCLONOL (FRENQUEL)

Frenquel is a piperdyl isomer of pipradiol hydrochloride (Meratran). It was found very effective in alleviating the experimental psychoses produced by mescaline sulfate and lysergic acid diamine. Because these experimental psychoses somewhat suggested schizophrenic episodes, it was felt that this drug might have a similar effect upon schizophrenic hallucinations and delusions. The initial work done by Fabing[1] at Cincinnati was most encouraging, but few people[2] have been able to duplicate his work. Rinaldi[3] stated it was most helpful in acute schizophrenic episodes, in other acute transient delusional states, and in postoperative confusional states. A group of individuals using this medication met in April 1956 and were almost unanimous in finding that the oral use of this medicine to be of no avail. It was then suggested that the difficulty was in using it orally instead of intravenously. I have subsequently prescribed it intravenously and still found it to be of no avail, even when used in acute situations. All seem agreed that it is of no value in the chronic schizophrenic. It may be that this drug will prove to have some value, but at present the most that can be said is that it does not cause any deleterious side effects.

RAUWOLFIA

Rauwolfia and related compounds were introduced in 1954-1955. In institutionalized patients Rauwolfia greatly reduced hyperactivity and aggressivity. However, in the greater number of anxious persons who were managing to adjust with varying success outside of hospitals, response was not as gratifying. Marked hyperactivity and aggressivity had not been their chief problems. The drug slowed them physically and mentally without solving the underlying problems. Reduction in activity is often quite disturbing to persons who have neurotically determined needs to be very active and constantly productive or to persons who realistically must do considerable physical or mental work, such as a mother of a large family or a business executive. In addition, the drug frequently causes unpleasant nasal stuffiness and occasionally aggravates depressions. Therefore, as a drug to produce psychologic peace, Rauwolfia compounds leave much to be desired and have been totally discarded from my practice.

PHENOTHIAZINE COMPOUNDS

Probably the best known member of this group today is chlorpromazine (Thorazine). Initially, there was optimism concerning its curative abilities. Subsequent critical controlled studies have shown that it is very helpful in controlling agitation and combativeness but that it is otherwise rather ineffective in either psychotic or neurotic individuals. Side reactions, including jaundice, allergic reactions, parkinsonism, and aggravated depressions occur in up to 25 per cent of treated patients making it too dangerous for use except in special cases. A new analogue, Compazine (proclorperazine), is just being introduced with claims of lower toxicity. From my limited observations Compazine is much less potent and relatively ineffectual in disturbed patients. It may be helpful in mild anxiety states.

Another member of this group is promazine (Sparine) in which the chlorine

radical has been omitted. This drug is available in tablets of 25 mgm., 50 mgm., and 100 mgm. and in an injectable form for either intravenous or intramuscular administration. I have also been using this medication in a capsule form made up so that one cannot tell the difference between any of these strengths nor of a corresponding placebo. According to animal experimentation, it was expected that larger doses of this drug than of chlorpromazine would be necessary, but I have found it of about equal effectiveness milligram for milligram. The dosage is not fixed and patients have been maintained on as much as 800 mgms. daily for five months without untoward effect. However, increasing the dosage beyond 400 mgm. per day usually does not prove worth-while.

Twenty-two patients suffering from many types of nervous disorder, mostly chronic psychoneuroses, were given promazine. Of the twenty-two, thirteen appeared to be helped, but seven of these felt just as well on a placebo. Of the six who could be said to have been helped by the medication, three were suffering acute disturbances with marked hyperactivity. aranoid delusions in two of these three were not relieved by the medication, but were relieved by electro-shock therapy. Among the other three persons helped was a chronic obsessive-compulsive housewife with a great deal of tension. She stated, "The medicine slows me down, relaxes me — I don't drive myself so." However, she continued to have many of her other complaints. Another obsessive person retained her obsessions but was less jittery. And finally, a disorganized ambulatory schizophrenic woman became more relaxed and more effective. Three patients developed weird "hysterical" symptoms upon taking the drug and also upon taking the placebo, so that nothing can be said concerning the efficacy of the medication in these individuals. Previously I have seen the hypomanic behavior of a manic-depressive executive decreased to a point where he was able to continue his normal duties. In such cases, the dosage must be adjusted frequently according to the severity of the hypomania.

Promazine has also proven helpful in quieting the acutely psychotic hyperactive individual, the acutely disturbed alcoholic, and the drug addict during the period of removal from the drug. Occasionally it will also be helpful in the more chronic disturbances. This drug will potentiate barbiturates so that their concomitant use must be watched closely. The drug also causes hypotension. Here it should be noted that epinephrine should not be used to alleviate this, but rather nor-epinephrine. So far, somnolence has been the only side reaction and this may be controlled by reducing the dosage. Promazine appears to be more desirable than Chlorpromazine and the results appear comparable.

MEPROBAMATE

On radio, television, and in various publications Meprobamate has been described as "the happy pills"; never has a drug been so widely demanded by the populace. It has been advertised to relax skeletal muscles, to produce a mild anticonvulsant activity, and primarily to tranquilize without sedating. Our experience with psychiatric patients fails to indicate that such enthusiasm is warranted. We have found it too mild to control effectively acutely disturbed individuals. In 10-15 per cent of the chronic anxiety or tension states, obsessional neuroses, or conversion reactions we did find it helpful but the majority of patients do not show any more improvement than with a

placebo. They may improve temporarily only to have their symptoms return shortly and to discover that, like the many other remedies they have tried, Meprobamate is not solving their problems and giving peace.

Meprobamate has so far been free of serious side reactions. An occasional patient may developed some dermatologic response, complain of blurring of vision, or complain of being too drowsy (despite the statement that they "tranquilize without sedating"). On rare occasions, patients have reacted with increased excitement. With large overdoses a person becomes completely flaccid and deeply comatose for as long as forty-eight hours. If an adequate airway is maintained and fluid balance is preserved, he will, with no other treatment, gradually return to normal. There has recently been a report indicating that the drug may be definitely habit forming in a small per cent of users and lead to excessive self-medication, somnolence, or a state resembling intoxication. Some of these persons have exhibited mild withdrawal symptoms when the medication was withdrawn. This does indicate that supervision is necessary when giving this medication. Certainly, it is a drug that might be tried, but with the knowledge that only a small per cent are really going to benefit.

Summary:

New medications to reduce anxiety are appearing daily. The clinical responses to a few of these are reported. None of these drugs are cures but may be useful crutches. The patient should always be evaluated to determine if psychotheraphy might not be more helpful in a curative direction.

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ETIOLOGY OF SPONTANEOUS SUBARACHNOID HEMORRHAGE*

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The term "subarachnoid hemorrhage" is misleading whether or not the adjective "spontaneous" is added to it and owes its popularity to the presence of blood in routine examinations of C.S.F.; but this fact provides no indication as to the source, and does not exclude bleeding in other areas or into other spaces. Spontaneous means nontraumitic and cannot be equivalent of "idiopathic" or "causeless".

The meningeal hemorrhages constitute a complication of other types of lesions. They are simply an event of the pathological picture, generally if not always the last. Similarly to the other forms of intracranial hemorrhage they result from a variety of conditions. The bleeding comes from arteries, veins, capillaries, or sinuses. The vessel walls can be damaged by trauma or diseases. Under the latter are included heterogenous conditions ranging from gross vascular lesions to minimal and obscure processes.

The separation of the subarachnoid hemorrhage from the other intracranial forms of hemorrhage is more artificial than real. The division into ventricular, cerebral, and meningeal (subarachnoid and subdural) types is commonly accepted; yet, any of these frequently occur in association. A "pure" subarachnoid hemorrhage is a relative rarity. The presence of blood in the cerebrospinal fluid constitutes no proof of its meningeal origin but only an indication of how it has leaked. Often subdural hemorrhage bursts through the torn fragile arachnoid, or subarachnoid bleeding resulting from cerebrifugal spread of the hemorrhage, and at times, the subarachnoid hemorrhage is confined to its own system. It is to this group that we intend to refer more specifically here.

Subarachnoid hemorrhage has a wide etiology. Because some cases are obscure, the well established causes of the majority should not be underestimated. For obvious reasons it will be very difficult to distinguish hemorrhagic leptomeningitis from leptomeningeal hemorrhage as well as the pial and subpial varieties.

If all cases of presence of blood in the subarachnoid space are considred, Courville has shown that more than half are due to external trauma, whereas many others occur during the neonatal period or as a result of extension to the ventricular system of a parenchymatous cerebral hemorrhage. Exclusion of such cases will leave a group in which the picture of "spontaneous subarachnoid hemorrhage" will be recognized.

Spontaneous subarachnoid hemorrhage has been used to designate the clinical condition in which the patient is seized with a sudden, unexpected and usually unexplained attack of severe pain in the head. This picture has been known since the middle of the 19th century when Wilks (1859) gave a brief account of the post-mortem examination of four cases, and Gintrac (1869) who in his book "Maladies de l'appareil nerveux" includes a chapter upon meningeal hemorrhages including thirty-four cases

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of spontaneous subarachnoid hemorrhage, thirty-two previously presented and two of his own. Bramwell (1886) appears to have been one of the first to associate this condition with a ruptured intracranial aneurysm and described what he termed meningeal hemorrhage following rupture of an aneurysm at the carotid termination. It was not until much later that it became generally recognized that spontaneous subarchnoid hemorrhage was of aneurysmal origin. This was due to the work of Symonds (1923-1924) and his detailed description of spontaneous subarachnoid hemorrhage which awakened interest in this important problem. Since then the literature on intracranial aneurysm has assumed enormous proportions and intracranial aneurysms have migrated from the post-mortem room where they were often a chance finding to the bedside.

Anatomical considerations: The arachnoid membrane according to Froin may be considered as consisting of two layers: parietal and visceral. The parietal layer consists of a sheet of endothelial cells lining the internal surface of the dura mater. The visceral layer consists of a thin, transparent sheet of connective tissue covered with endothelial cells which, upon its external surface, is separate from, but lies closely applied to, the parietal layer. Internal to this layer is the pia mater, which is attached to, and therefore follows exactly, the surface of the brain and spinal cord. The potential cavity existing between the parietal and visceral layer of the arachnoid is commonly known as the subdural space. The space which lies between the arachnoid and the pia mater is the subarachnoid space. This latter is normally occupied by the C.S.F. Although it is a true space in the sense that all parts of it are in direct communication with one another, it is to some extent broken up by innumerable trabeculae passing between the arachnoid and pia mater.

The arachnoid is closely applied over the cerebral surface and convolutions but it bridges the sulci. In the base the arachnoid is loosely applied to the brain with large spaces — cisternae — of fluid in free communication with the spaces around the cerebral vessels and with the subarachnoid spaces of the spinal cord.

Into the subarachnoid space blood may enter from different sources:

a. The parietal layer may be ruptured by blood into the subdural space.
b. Hemorrhage from the brain may rupture through the pia mater into the subarachnoid space.
c. Cerebral hemorrhage may rupture into a ventricle and thus gain access to the subarachnoid space (cerebro-meningeal hemorrhage of Froin).
d. Hemorrhage may come from a vessel rupturing in the subarachnoid space.

The hemorrhage into the cistern can extend freely into the spinal subarachnoid space. Over the surface of the brain the narrow sulci often prevent a rapid extension of the blood into the cisterns and in this way may permit local accumulations of blood to expand until the hemorrhage ruptures into the cerebrum (Froin's meningocerebral hemorrhage). In cases of basal hemorrhage the extravasation may spread widely over the cerebral sulci and into the spinal subarachnoid space from basal cisterns.

Incidence:

The incidence of spontaneous subarachnoid hemorrhage varies according to the different authors. This variation is explicable on the basis of the material studied.

Table I

Incidence of Subarachoid Hemorrhage

Authors	Total Cases	No. Deaths of S.S.H.
Martland (1939)	2500 sudd. death	54 (2%)
Moritz and Zamcheck (1946)	1200 " "	60 (5%)
Helpern and Rabson (1950)	2030 " "	95 (4.7%)
Adams and Cohen (1947)	329 C.V.A.	19 (5.8%)
Russell-Brain (1954)	200 C.V.A.	30 (15%)
Russell D. S. (1956)	461 autopsies (intracr. hem.)	96 (20.8%)

Ohler and Hurwitz (1932) reported that in the Boston City Hospital in an eighteen month period there were three hundred and fifty-three cases of cerebral vascular accidents and twenty-four cases (6.7%) of subarachnoid hemorrhage.

Adams and Cohen (1947) in a study of incidence of proved vascular diseases of the brain in three hundred and twenty-nine autopsied cases found that arteriosclerosis and encephalomalacia (thrombosis or infarction) was responsible in 41% and meningeal hemorrhage (ruptured aneurysm) occurred in about 5.8%.

Russell-Brain (1954) mentioned that the number of deaths from vascular lesion of N.S. in England and Wales according to the Registrar General's figures in 1942 was 56.048 and in 1952 it was 69.388 or approximately 14% of the total deaths. In two hundred cases of cerebrovascular disease, one hundred from hospital wards and one hundred private patients, Russell-Brain found that hypertension was present in approximately 50% of the cases. Subarachnoid hemorrhage occurred in thirty of the patients (15%).

Kristiansen (1956) in a clinical and radiological evaluation of spontaneuos subarachnoid hemorrhage at the general hospital of Oslo (population 400,000 inhabitants) during the five year period (1950-1954) reported that there had occurred one hundred and thirty cases of spontaneous subarachnoid hemorrhage, and its incidence in relation to the general population of Oslo is calculated in three cases per 50,000 of living persons.

Martland (1939) analyzed a group of two thousand five hundred cases of sudden death and of these fifty-four (2%) were due to subarachnoid hemorrhage.

In a survey of 40,000 autopsy protocols in the Armed Forces Institute of Pathology (1942-1946) Moritz and Zamcheck found one thousand two hundred cases of sudden death in apparently healthy soldiers. Three hundred and fifty of these were due to heart disease, one hundred and ten to meningococcemia, one hundred and forty to obscure causes, and ninty-one (7%) to intracranial hemorrhage. Sixty of this latter group were subarachnoid hemorrhages from proved or presumed congenital aneurysms.

A statistical survey made by Helpern and Rabson (1950) in the office of Chief Medical Examiner, New York City, found that subarachnoid hemorrhage caused 4.7% of two thousand thirty cases of sudden death (nontraumatic). This represented 25.7% of the three hundred and seventy fatalities from diseases of the N.S.

These figures are influenced by the type of hospital from which they are reported; if they were gathered in a general hospital, more cases of cerebral hemorrhage most likely would be reported, while in a specialized neurosurgical service, a greater proportion of cases of subarachnoid hemorrhage would be admitted. In the anatomical series one would expect a greater number of cases of intracerebral hemorrhage, as the prognosis of this condition is more serious than subarachnoid hemorrhage alone.

It seems reasonable to conclude that subarachnoid hemorrhage acounts for about 8% of the cerebral vascular disease (Walton) and it is less common than intracerebral hemorrhage of hypertensive or arteriosclerotic origin. It is also an important cause of sudden death.

Series of cases of spontaneous subarachnoid hemorrhage resulting from ruptured intracranial aneurysms are compiled in Table II. From the analysis of the data collected from general and specialized services, one can conclude that ruptured intracranial aneurysms are responsible for subarachnoid bleeding in about 34% to 60% of the cases. This finding seems to be in contradiction with the most general assumption that ruptured aneurysms are responsible for about 90% of this syndrome.

Table II

Incidence of Intracranial Aneurysms in S.S.H.

(Clinical-Path. Series)

Authors	No. Cases S.S.H.	Suspected or Proved Aneurysms
Timberlake and Kubik (1952)	422	280 (60.6%)
Hamby (1952)	130	44 (34.6%)
Walton (1953)	312	65 (20.8%)
Walsh (1956)	461	249 (54%)
Kristiansen (1956)	130	58 (43%)
Bebin and Currier (1956)	713	243 (34%)

Etiology:

However, aneurysmal or angiomal rupture are considered the commonest cause of spontaneous subarachnoid hemorrhage. From time to time this condition has been described as occurring in many other pathological conditions. In such cases recognition of the etiological lesion is important from the standpoint of therapy.

Among the specific causes of spontaneous subarachnoid hemorrhage are included numerous conditions which are summarized in the following table.

Table III
ETIOLOGY OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

A. INTRACRANIAL
1. Aneurysms
2. Angiomas and other vascular malformations
3. Arterial rupture without aneurysm
4. Neoplasms
5. Blood dyscrasias
6. Dural and venous thrombosis
7. Inflammatory conditions of the brain and meninges
8. Miscellaneous disorders

B. INTRASPINAL
1. Angiomas and other vascular malformations
2. Aneurysms
3. Neoplasms
4. Blood dyscrasias
5. Polyarteritis nodosa
6. Generalized toxi-infective conditions

When one considers all the lesions that can produce bleeding in the subarachnoid space, a very diverse cause can be obtained. Courville listed the causes of one hundred and forty-nine cases found in one thousand five hundred autopsies. In this group were included thirty-five cases of injuries and diseases of the new born. Sands made the study of one hundred and twenty cases of subarachnoid hemorrhage in which 7.5% he attributed to trauma; 25% to arteriosclerosis; 13.6% to infectious diseases; 20% to intracranial aneurysm; and 22% to miscellaneous causes which included brain tumors, blood dyscrasias or were secondary to intracerebral hemorrhage.

MISCELLANEOUS CAUSES OF SUBARACHOID HEMORRHAGE

Focal vascular necrosis
Polyarteritis nodosa
Anaphylactoid purpura
Hemorrhagic nephritis
Acute rheumatism
Sunstroke
Alcoholism
Insulin therapy
Metrazol administration

Gull already noted that the apparent rarity of intracranial aneurysm as a cause of hemorrhage was probably due to the fact that they were not looked for specifically, and he stated that in "young persons dead of apoplexy if a large effusion of blood is

found specially over the surface of the brain in the meshes of the pia mater, the presence of an aneurysm is probable." The faliure to find an aneurysm during the routine post-mortem examination does not exclude that probability as it has been pointed out by Schmidt (1931). He believed that the great majority of, and perhaps all, fatal spontaneous subarachnoid hemorrhages were due to aneurysms. Richardson and Hyland also emphasized the care necessary at necropsy to exclude an aneurysm as the cause of an otherwise unexplained hemorrhage. Hamby in a study of the records of one hundred and thirty patients with spontaneous subarachnoid hemorrhage excluding as cause of bleeding tumors, intracerebral hemorrhage, trauma, and blood dyscrasias found that out of forty-seven cases, the cause of bleeding was a ruptured aneurysm in 44 (93%).

It is evident that subarachnoid bleeding can occur in a variety of diseases. The analysis of series of cases leads to the conclusion that the spontaneous subarachnoid hemorrhage ordinarily is from a ruptured aneurysm of one of the arteries in or near the circle of Willis.

Since the advent of angiography it has been possible to subdivide cases of subarachnoid hemorrhage into three main groups: a. cases in which an aneurysm can be displayed; b. cases harbouring an angioma or other vascular malformations and, c. cases in which no causal lesion can be demonstrated excluding all cases of spontaneous subarachnoid hemorrhage due to general disease processes.

Intracranial aneurysms:

Krayenbuhl gives Morgani (1761) credit for the first description of two aneurysms of the posterior cerebral arteries and according to Fearnsides, Biumi (1765) of Milan was the first to describe an aneurysm found at autopsy. Although aneurysms arising from the cerebral arteries have been recognized for a century or more, it is only during recent years that their clinical manifestations have become fully documented and their life history appreciated.

The papers on Beadles (1907) and Fearnsides (1916) were largely of pathological interest. Symonds in 1924 gave a detailed description of the clinical picture of spontaneous subarachnoid hemorrhage which he related causally to a rupture with a cranial aneurysm, and since the introduction of the angiography by Egaz-Moniz (1927), the interest in intracranial aneurysms has developed enormously. Proof of this fact rests in the excellent monographs and books on this subject, thus the book of Hamby on intracranial aneurysm dealing with symptomotology, signs, treatment, and prognosis according to the exact anatomical position of the aneurysm on the intracranial vascular tree.

Incidence:

Even though numerous statistical analyses have been published on this subject, it is very difficult to assess the incidence of intracranial aneurysms. The difficulties arise from the fact that until recent years this lesion was only or almost only described in post-mortem material.

In 1890 Pitt reported that in nine thousand autopsies at Guy's Hospital between 1869-1888, nineteen cases (0.25%) of embolism and aneurysm occurred. Turnbull,

Table IV

Incidence of Intracranial Aneurysms
(Autopsy Series)

Authors	No. Autopsies	No. Aneurysms
Pitt (1890)	9000	19 (0.2%)
Turnbull (1918)	6,751 (compl.) 4,547 (head)	42 (0.92%)
Mitchell and Angrist (1943)	3080	42 (1.1%)
Courville (1945)	30,000 (50% head)	96 (0.58%)

pathologist of the London Hospital, reported that in 1913 six thousand seven hundred and fifty-one autopsies with 4,547 examinations of the head in which 1.36% of aneurysms of the aorta were found and forty-two (0.92%) of intracranial aneurysms were identified.

Mitchell and Angrist in 3,080 routine autopsies found forty-two (1.1%) aneurysms in thirty-six patients. Courville in a series of 30,000 autopsies in 55% of which the head was examined, found ninety-six (0.58%) intracranial aneurysms.

Richardson and Hyland found forty (0.87%) intracranial aneurysms in 4,618 autopsies.

From the consideration of this data it is difficult to situate the incidence of intracranial aneurysm in the general population. A percentage of 0.5-1% is considered by Hamby as the most reasonable.

Sex and Age:

In general it is accepted that more intracranial aneurysms occur in women than in men. The statistical data seems to prove this assertion. McDonald and Korb found five hundred and seventy-four women and five hundred and nineteen men; Richardson and Hyland twenty-two women and eighteen men; Hamby fifty women and forty-one men; Falconer fifty-six women and forty men.

Concerning the age of presentation of this condition, Dandy made a generalization that is in agreement with most reported series. Few cases are found under the age of twenty; thereafter, the decades contain about an equal number until the age of seventy after which they decline.

Dandy's youngest patient was eight years old and his oldest eighty-one. Dial and Maurer reported the case of a two year old child and numerous other cases have been reported in childhood. In the McDonald-Korb series (1125 intracranial aneurysm) the youngest patient was one and a half years old and the oldest eigthy-seven. They gave the age distribution of five hundred and forty-five intracranial aneurysms: under twenty years 11%, between twenty-one years of age and forty 35%, and over forty 54%. One may assume that about half of the cases of intracranial aneurysms occur after the age of forty years.

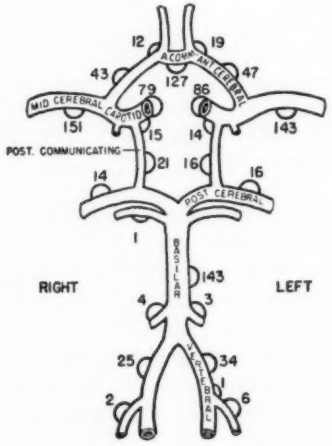
Location of Aneurysm:

The literature in this respect is very extensive and numerous careful compilations have already been made and analyzed from several points of view. The following table and diagram summarizes the incidence of aneurysmal formations in the various cerebral arteries.

Table V

Location of Aneurysms

Authors	Total	Carotid tree	Vert-Bas. tree
McDonald and Korb (1939)	888	735 (83%)	153 (17%)
Riggs and Rupp (1943)	172	155 (90%)	17 (10%)
Hamby (1952)	93	79 (84%)	14 (16%)
Falconer (1954)	110	105 (95%)	5 (5%)
McKissock and Walsh (1956)	249	213 (85%)	15 (6%)



Distribution and location of 1125 intracranial aneurysms collected by McDonald and Korb.

From the statistical information some general conclusions of practical clinical interest can be made. Almost all the intracranial aneurysms are situated at an angle branching off a major artery. Three principle sites are preferential ones: a. the junction of the internal carotid artery and its posterior communicating branch; b. the junction of anterior communicating artery with either anterior cerebral arteries, and c. the first point of branching of the middle cerebral artery with the fissure of Sylvius.

As these sites are all in the carotid arterial tree or in the anterior half of the circle of Willis (83%), they are more likely to be demonstrated by arteriography and more accessible to surgical treatment.

Multiple aneurysms:

They occurred according to Dandy in approximately 15% of his cases. He reported one hundred and thirty-three in one hundred and eight patients. Riggs and Rupp found 28% of multiple aneurysms in one thousand four hundred and thirty-seven autopsies. One of their cases had as many as five aneurysms. Hamby found ninety-four aneurysms in eighty-six patients; eight of these (9.3%) had multiple aneurysms.

Types of aneurysms:

Various types of intracranial aneurysms have been described, the etiology of which may be evident or extremely obscure and elusive. Different classifications have been suggested. Walsh and King provided the following descriptive working classification.

Table VI

INTRACRANIAL ANEURYSMS

I. ARTERIOVENOUS ANEURYSMS
   a) Carotid cavernous: Chiefly fistulas between internal carotid artery and cavernous sinus.
   b) Cirsoid, including the cerebral arteriovenous fistulas and malformations.

II. ARTERIAL ANEURYSMS
   a) SACCULAR
      1. Miliary — the result of atheromatous changes.
      2. Mycotic — through deposition of septic emboli in arterial walls.
      3. Post-traumatic.
      4. Atheromatous of Circle of Willis.
      5. Congenital — "berry" aneurysms of Circle of Willis and other cerebral arteries.
   b) FUSIFORM — chiefly of internal carotid, vertebral and basilar arteries.

Of these different types of intracranial aneurysms we will consider briefly only the three most common types: congenital, atherosclerotic, and mycotic.

Congenital aneurysms: They constitute the majority of intracranial aneurysms. The significance of developmental defects and arteriosclerosis in aneurysmal formations in the elderly subject with hypertension and atherosclerosis is difficult to evaluate. Bremer's and Padget's theory of their development from persistent remnants of the embryonic vascular network seems very attractive. It may well be that almost all intracranial aneurysms, excluding the mycotic or infective group, have a developmental basis in the form of defects in the media at arterial junctions, but secondary factors of hypertension, arteriosclerosis or focal degeneration of the arterial wall play an important part both in the evolution of the aneurysm and its subsequent rupture. From the greatest incidence of rupture in the fourth and fifth decade and prevalence of demonstrable degenerative changes in the wall of the sac one can conclude that these factors are of great significance, but the basic pathology of a congenital defect in the

media is supported by the demonstration of associated defects of a similar character without degeneration and at sites remote from branching. The medial defect is of developmental origin, but the gap in the elastic membrane is due to degenerative changes. The precise combination of these lesions varies from case to case and Carmichael (1950) states that no valid distinction can be made between the so-called congenital and arteriosclerotic aneurysms.

Arteriosclerotic aneurysms of the "pure" type are relatively uncommon. Severe atherosclerosis may give origin to fusiform aneurysmal dilatations of arteries of the circle of Willis and particularly of the basilar and internal carotid arteries. Richardson and Hyland (1941) found two arteriosclerotic aneurysms both fusiform and involving the basilar artery in their series of fifty-three cases. Dandy found twenty-two of his type and regarded the saccular or "berry" aneurysms as congenital and the fusiform aneurysm of the larger arteries as arteriosclerotic in origin.

Mycotic aneurysms: These aneurysms are due to impaction in a cerebral vessel of infective emboli with subsequent softening of the vessel wall. The complication occurs during the course of a septicemia usually accompanying bacterial endocarditis though these aneurysms may result from other forms of chronic septicemic conditions. They are small saccular aneurysms showing marked inflammatory changes in their wall. They tend to occur in the distribution of the middle cerebral artery. They may be found at a distance from the circle of Willis and in the substance of the brain. Mitchell and Angrist found in their series that eleven of forty-two aneurysms were mycotic. Seven were produced by subacute bacterial endocarditis. The usual clinical manifestation of mycotic intracranial aneurysm is a sudden cerebro-vascular accident such as subarachnoid hemorrhage, sudden hemiplegia, etc., occurring in a well established diagnosis of infective disease.

Other types: Syphilitic intracranial aneurysms are rare. Fearnsides (1916) found no evidence of syphilis in any of his fifty-one autopsy cases and Turnbull (1918) did not see any example of a syphilitic aneurysm in over six thousand necropsies. Richardson and Hyland stated that lues causes 90% of aneurysms elsewhere in the body but plays little role in the formation of cerebral aneurysms. Syphilitic infection produces obliterative arteritis and thrombosis of smaller muscular and elastic arteries such as the cerebral arteries which explains the rarity of cerebral aneurysms of syphilitic origin. There are, however, a few cases of this type of the basilar artery on record.

Aneurysmal dilatation of the smaller vessels may occur in polyarteritis nodosa and the cerebral vessels are occasionally affected. The necrosis of the vessel wall especially the media with inflammatory changes in the adventitia resulting in narrowing of the lumen and thrombosis with subsequent infarction and aneurysmal formation may cause subarachnoid bleeding.

Angiomas and other vascular malformations:

Recently the knowledge of the clinical and pathological features of intracranial angiomas has increased considerably. It is now realized that far from being rare, as were thought, these developmental vascular anomalies are a frequent cause of subarachnoid hemorrhage, cerebral hemorrhage and symptomatic epilepsy.

The term angioma suggests that these lesions are tumors. It is actually almost universally accepted that these are not true neoplasms. These lesions are considered as the second most common cause of subarachnoid hemorrhage accounting for a possible 5-10% of cases according to Falconer (1954). He found twelve instances in one hunrded and forty-eight patients suffering from spontaneous subarachnoid hemorrhage. Walsh (1956) indicated an incidence of fifty-three cases (11%) in four hundred and sixty-one of subarachnoid hemorrhage. Recently Paterson and McKissock (1956) surveyed the symptomotology and treatment of one hundred and ten cases of intracranial angiomas. Of these, sixty-three (57%) of their patients were males and forty-seven (43%) were females. In the majority of instances the diagnosis was confirmed by angiography and in some at the operation. In ninety-two patients an angioma was found in one or the other hemisphere. In one case the angiography suggested bilateral angiomas.

The most common site is in the middle part of the hemisphere (sylvian point) sixty-one cases; then follow in frequency the posterior group (parieto-occipital region) twenty cases, and anterior group (frontal or fronto-parietal region) eleven cases. In the central region (thalamus, basal ganglia, and midbrain) there were nine cases. Others were found in corpus callosum, three; posterior fossa, three; intraventricular, two; and orbital, one.

Dorothy Russell (1954) classified these lesions as hamartomas considering the following groups:

1. Telangiectasies: These are of essentially capillary structures and are most often found in the pons. Spontaneous subarachnoid hemorrhage is rarely recorded.
2. Cavernous hemangioma: They favor a subcortical site in rolandic area or basal ganglia.
3. Arteriovenous hamartomas: They are a common source of spontaneous hemorrhage (subarachnoid and intracerebral).

In the Paterson and McKissock series spontaneous subarachnoid hemorrhage was the commonest sign and was encountered in forty-six patients or 42% of the total (one hundred and ten patients). In forty-two instances a subarachnoid hemorrhage occurred with or without signs indicative of an association intracerebral hemorrhage. In four cases the evidence favored the occurrence of intracerebral hemorrhage. Other common symptoms are epilepsy, twenty-nine patients (26%), periodic migrainous headache, sixteen patients (15%), and progressive hemiparesis, eight patients (7%). These lesions manifest themselves in early life or in adulthood. The average age of onset of symptoms is twenty-four years as nearly 70% of patients had their first symptoms before they were thirty, the majority in their second or third decades (Paterson and McKissock). The youngest patient was an infant of one year having seizures and the oldest a man of fifty-seven when he noticed that his first symptom was the onset of numbness of the left fingers.

The classical type of these lesions is a mass of arteries and veins in the meninges which burrows into the subjacent brain and may eventually rupture into the lateral ventricle or produce a hematoma in the cerebral substance. Small lesions of this kind

are found at: 1. *cerebral convexity,* sometimes concealed in the depths of a sulcus, perhaps involving the subjacent cortex or subcortical white matter. Microscopically they are made up of enlarged tortuous and malformed arteries and veins. Eleven of the twenty of the cases described by D. Russell were of this type. 2. *central* predominantly of venous type are found in the white matter region of the choroid plexus of the lateral ventricle, the veins of corpus striatus and the small veins of Galen. Five cases of Russell belong to this group. 3. *cerebellar,* they occupied the central white matter and could measure a few millimeters in diameter. This group included six cases out of twenty of Russell's series.

In the Sturge-Weber-Dimitri syndrome in which an angioma of the brain and meninges is associated with a facial angioma (nevus flammeus), bleeding may occur originating a subarachnoid hemorrhage. Walton (1953) reported a case of multiple hereditary hemorrhagic telangiectasia as a cause of spontaneous subarachnoid hemorrhage.

Arterial rupture without aneurysmal formation:

In the literature there is an occasional reference to cases in which subarachnoid hemorrhage resulted from a rupture of an atherosclerotic artery at the base of the brain (Walton).

In the series reported by Taylor and Whitfield (1936), one patient died from subarachnoid hemorrhage resulting from rupture of apparently healthy vessels at the bifurcation of the internal carotid artery. A similar case of such an uncommon event was described by Bagley (1928).

Intracranial neoplasms:

Spontaneous subarachnoid hemorrhage in brain tumors is a very rare eventuality. In the one hundred and twenty-four cases of subarachnoid hemorrhage reviewed by Symonds, only two could be attributed to intracranial tumor or cyst. Globus and Sapirstein in a study of ninety-four cases of brain tumors found some evidence of subarachnoid bleeding in twenty-one patients. In the majority of these cases the C.S.F. showed xanthochromia only in a small number (six cases of metastatic carcinoma). It was frankly bloody.

Profuse subarachnoid hemorrhage occurs rarely as the first symptom of a cerebral glioma and meningiomas; however, there are a few examples of such an event (Burges, Echols and Rehfeldt, Walton).

Evident bleeding into the subarachnoid space occurs relatively often in cases of metastatic carcinoma to the brain, particularly in bronchogenic metastatic carcinomas.

Primary or secondary malignant intracranial melanomas are liable to produce sudden subarachnoid hemorrhage that may cause confusion with aneurysmal rupture. The C.S.F. in these cases was grossly bloody in the majority of cases and xanthochromic in several. According to Vigneras sixteen of the thirty-five cases of metastatic melanoma of the brain showed bloody or xanthochromic C.S. In one melanin was demonstrated in the C.S.F. and also melanuria. In the Schnitker and Ayer series there was evidence of subarachnoid hemorrhage in twenty-six (46%) of fifty-six cases of intracranial melanomas.

Northfield and Russell mentioned that death due to subarachnoid hemorrhage occurred in two cases of osteochondroma of the base of the skull observed by them. We had the occasion to perform an autopsy on a case of subarachnoid hemorrhage due to chordoma of the basis of the sphenoid.

List and associates suggested that rapidly growing pituitary adenomas may outstrip their blood supply, thus producing infarction. When this occurs the neoplasm becomes a rapidly swelling hemorrhagic mass which may produce bleeding into the subarachnoid space.

Blood dyscrasias:

Many blood diseases may be complicated by spontaneous subarachnoid bleeding. These include: hemophilia (Gintrac, Timberlake and Kubik), pernicious anemia (McMullen), aplastic anemia, leukemia and agranulocytosis (Strauss). It should be mentioned here that subarachnoid hemorrhage occurring during liver disease is accompanied by severe jaundice and probably subarachnoid bleeding may occur during anti-coagulant therapy.

Dural and venous thrombosis:

Attention to the occurrence of meningeal hemorrhage in cases of thrombosis of the superior sagittal sinus was directed by Gintrac, Hayem, Froin, Klein and Lereder; they described a similar case in which subarachnoid hemorrhage resulted from thrombosis of the right lateral sinus and internal jugular vein. In only one of the eleven cases of venous thrombosis during pregnancy, described by Kendal, did the C.S.F. show presence of blood. Walton described a case of subarachnoid hemorrhage in an infant five months old due to thrombosis of the sagittal sinus resulting from acute otitis media.

Inflammatory conditions of the brain and meninges:

The early accounts by Gintrac, Hayem, and Froin emphasized the association of subarachnoid hemorrhage with acute bacterial infections, infective fevers, anthrax, meningitis, and meningoencephalitis. Sands referred to cases in which tonsillitis, meningococcal septicemia, and brain abscess respectively were complicated by the occurrence of subarachnoid hemorrhage. It has been suggested that in cases of this nature a large vessel or numerous small vessels are eroded by the fulminating inflammatory process (Walton).

Biber reported subarachnoid hemorrhage occurring in cases of tuberculous meningitis in which the underlying pathological process is an arteritis with dilatations in the meningeal vessels. However, recent reports of large series of cases of tuberculous meningitis failed to support the assertion. The thrombosis and the resulting infarction following the vascular occlusions are more common and hemorrhage the exception.

Syphilis, contrary to general accepted assertions in early literature, is rarely a cause of subarachnoid hemorrhage.

Arteritis produced by aspergillosis of the brain has produced a typical subarachnoid hemorrhage in a case (McKee). Similar episodes have been recorded in relapsing fever (Demar and Walmsley). This raises the possibility that the mechanism of bleeding was due to generalized vascular changes rather than to the primary infection.

It is well known that subarachnoid hemorrhage may occur during the course of subacuate bacterial endocarditis. In this condition usually the hemorrhagic episode results from rupture of a mycotic aneurysm. However, in some rare cases of this disease subarachnoid hemorrhage is the initial manifestation before other symptoms of the disease have been recognized (Stein, Starrs). However, in certain cases in which patients died of cerebral vascular accidents in the course of subacute bacterial endocarditis, no aneurysmal dilation of the arteries can be demonstrated. Frequently the hemorrhage is primarily intracerebral with spread to the subarachnoid space. Martland has suggested that it is produced through the general toxic effect upon the vessel wall.

Miscellaneous causes of subarachnoid hemorrhage:

This constitutes a group of hetereogenous conditions resulting in subarachnoid bleeding.

Focal vascular necrosis resulting in subarachnoid hemorrhage and occurring in elderly hypertensive patients within a few days of uncomplicated abdominal operation was reported by Kernohan and Woltman in four cases. All were fatal and at necropsy the bleeding was found arising from rupture of a vertebral artery in two cases and a posterior inferior cerebellar artery in two. The microscopic examination of the arteries revealed that the rupture was due to a focal aseptic necrosis of the vessel's walls. That, according to the authors, had occurred as a result of thrombosis of the vasa vasorum.

Polyarteritis nodosa:

This disease occasionally involves the blood vessels of the brain with subarachnoid hemorrhage complicating its course (Wechsler, Foster and Malamund, Summers).

Bleeding into the subarachnoid space has also been described *anaphylactoid purpura* (Miller), in patients with hemorrhagic nephritis (Sands), and in patients with acute rheumatism. Walton suggested that it is possible that a general allergic vascular response was accountable for the subarachnoid hemorrhage in these conditions.

Other miscellaneous agents apparently concerned in the etiology of individual cases of subarachnoid hemorrhage include *sunstroke* (Bouquet, Doufor cited by Symonds); *scurvy* and *alcoholism* (Strauss and Tarachow). The same authors noted the presence of tuberculous diabetes and Hodgkin's disease in certain cases of subarachnoid hemorrhage. They suggested an etiologic relationship but it seems that association was only fortuitous. Finally, subarachnoid hemorrhage has also been reported in insulin therapy and Metrazol administration (Freed and Wofford, Pedersen).

Spontaneous spinal subarachnoid hemorrhage:

The spontaneous spinal subarachnoid hemorrhage is very rare and less widely recognized. The distinction of this condition from the intracranial spontaneous subarachnoid hemorrhage is not always easy and it is likely that patients with spontaneous spinal subarachnoid hemorrhage are sometimes thought to be suffering from the much commoner intracranial type of bleeding. A survey of the published reports shows that isolated cases of this form of spinal hemorrhage have been described usually in reviews of the spinal vascular abnormalities.

Subarachnoid Hemorrhage

The first observation of subarachnoid hemorrhage confined to the spinal theca was that of Duverney (1868) who described a case of a magistrate who died suddenly of a particular form of apoplexy. The autopsy of this case disclosed a normal appearance of the brain and its membranes, but a large hemorrhage filled the spinal subarachnoid space.

Vigneras, in his monograph upon this subject, remarked that when such hemorrhages occurred spontaneously, they could be attributed to syphilis, alcoholism, or hemophilia, but in many cases it was impossible to ascertain the cause. Other cases resulted from trauma or were secondary to neoplasms of the cord and meninges.

The clinical symptomotology of spinal subarachnoid hemorrhage falls conveniently into three groups (Hensen and Croft):

1. The results of the entry of blood into the spinal subarachnoid space: sudden and agonizing pain in the back "coup de poignard" of Michon; bilateral sciatica; strongly positive Kernig's sign.
2. Symptoms and signs of intracranial extension of the hemorrhage. These follow very rapidly when the hemorrhage is in the cervical region.
3. Symptoms and signs due to involvement of the spinal cord and nerve roots. These may result from the accompanying hematomyelia or the cord may be compressed by blood, blood clot or both.

Etiology:

1. *Spinal angiomas:* They are undoubtedly the commonest cause of spinal subarachnoid hemorrhage. Examples of this type have been published by Balk (1900), Wybur-Masson (1943), Walton (1953), and Hensen and Croft (1956). In the Hensen and Croft series of seven cases, the post-mortem examinations of three of their cases disclosed that two had vascular hamartomas (spinal angiomas). Nevertheless, hematorrachis is not always a common symptom of spinal angiomas. Sargurt (1925), Globus and Doshay (1929), Epstein, Beller, and Cohen (1949), and Brion, Netsky, and Zimmerman (1952) have published series of four, four, six and nine cases of spinal vascular anomalies respectively, all without subarachnoid hemorrhage. On the other hand, Trupp and Sachs (1948) had three examples of hemorrhage among their seven patients. Hematomyelia and hematorrachis may occur together Wyburn-Masson (1943), but they are frequently divorced. Hemorrhage from angiomas may be precipitated by trauma (Brion et assoc.).
2. *Aneurysms* are very rare in the spinal vasculature. One of the patients in Hensen and Croft's series died of an aneurysm of the posterior spinal artery.
3. *Neoplasms:* Krayenbuhl (1947), Roger, Paillas, and Duplay (1949), and Fincher (1951) have drawn attention to the occurrence of subarachnoid hemorrhage with intradural neoplasms. Ependymomas in the lumbar sac are the commonest spinal neoplasm to bleed. Spinal hemangioblastomas, though rare, may be a cause of subarachnoid hemorrhage because of their connection with the pia.
4. *Polyarteritis nodosa:* Hensen and Croft reported a case of spinal subarachnoid hemorrhage presenting periarteritis nodosa and found two other additional cases in the records of Bernhard Baron Institute of Pathology of London.

5. *Blood dyscrasias:* They are a rare casue of massive spinal subarachnoid bleeding. Yuhl (1925) reported a patient who suffered from spontaneous, subdural, and subarachnoid spinal hemorrhage while under treatment with Dicoumerol.
6. *Generalized toxi-infective conditions:* The occurrence of spinal hemorrhage in the course of typhoid fever has been mentioned. Syphilis, and alcoholism are of little importance in the etiology of this syndrome.

Summary:

Spontaneous subarachnoid hemorrhage usually results from rupture of an intracranial aneurysm, or less frequently a cerebral angioma (hamartoma). It can also occasionally result from a variety of pathological conditions. These in the intracranial variety of subarachnoid hemorrhage include: neoplasms, blood dyscrasias, venous thrombosis, inflammatory conditions, focal vascular necrosis, vascular allergy, and even insulin and Metrazol therapy.

Spinal subarachnoid hemorrhage is usually the result of vascular malformations of the spinal cord and meninges; occasionally it results from intraspinal neoplasm, and, more rarely from miscellaneous etiologic conditions.

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study with review of literature and report of an additional case, J. Nerv. & Ment. Dis. 87:45, 1938.

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ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

EFFECT OF DIHYDROCHOLESTERAL AND B-SITOSTEROL ON CHOLESTEROL ATHEROSCLEROSIS IN RABBITS. W. T. BEHER, G. D. BAKER AND W. L. ANTHONY. Circulation Res. 5:202, 1957.

Atherosclerosis was induced in rabbits by means of dietary cholesterol. Administration of dihydrocholesterol to these animals increased the initial rate of plasma cholesterol regression, but hindered the regression of total liver cholesterol. Dihydrocholesterol did not promote the regression of either the aorta lipid fractions or plaque areas.

Dietary dihydrocholesterol, fed to normal rabbits for a seven month period, resulted in the formation of aorta plaques, and in a general increase in all of the lipid fractions. There are data to suggest that dihydrocholesterol is deposited in the aortas. Extensive liver damage was noted in these rabbits fed dihydrocholesterol. Histological examination showed advanced cirrhosis and chemical analysis revealed increased total lipid cholesterol and B-sterols.

B-sitosterol proved to be nontoxic. Its administration did not result in aorta plaque formation or changes in liver or aorta lipid fractions. Moreover, it was just as effective as dihydrocholesterol in lowering total plasma cholesterol.

NARCOTIC ADDICTION AMONG PHYSICIANS. J. D. FOX. J. Michigan M. Soc. 56:214, 1957.

While the public is looking at its own narcotics problem, the physician, the man nearest to the narcotic needle, should not overlook the menace in his own medical bag. The following hints, if observed, will do much to reduce the 100 *new* doctor-addicts lost from our profession each year. (1) You are human, subject to the temptations of laymen. (2) Never let easy access to narcotics be an excuse for your first "shot". (3) Don't get overly tired and fatigued. When you are worn out, take a vacation. It's a lot safer, and a lot more fun. (4) Don't drink. Alcoholism can lead to drug addiction. (5) If you have surgery or become ill don't ever take narcotics on your own. Keep in mind what Benjamin Franklin said: "The man who treats himself has a fool for a doctor." (6) As a monitor against easy escape from an emotional problem, always think of your family, your future, and your prestige. Best of all, breathe a prayer for God to keep your hand off any narcotic during time of stress. (7) Take time to relax each day and meditate on the many blessings God has given you. This will "up" your spirits. Only depressed doctors take dope. Keep a happy mental outlook, and you do much to prevent the world's most insidious and most hopeless habit.

URETHROVESICOPUBIC RELATIONSHIPS IN THE FEMALE. 2. EFFECTS OF COITUS, PARTURITION, MENOPAUSE, AND UTERINE SUSPENSION. C. P. HODGKINSON. Am. J. Obst. & Gynec. 73:518, 1957.

Variable degrees of lasting attenuation, relaxation, and other sequelae of trauma

are hallmarks of parturition in the birth canal. By modern obstetrical standards, they signify the ransom price of pregnancy. How, and to what possible end, these changes affect the urethrovesicopubic relationship are questions which have fired the imagination of gynecologists for years. Of more fundamental importance are the subtle changes in urethrovesicopubic relationships which develop in married nonparous women as they approach and transcend the menopause. The comparison and demonstration of changes in urethrovesicopubic relationships by these influences are the intent of this study. Increasingly impressive sequelae are shown in the following groups. Group I, non-parous, Group II, normal," parous patients, Group III, uterovaginal prolapse, Group IV urinary stress incontenence, Group V, urethrovesicopubic relationships and Guilliam-Doleris uterine suspension.

THE EMERGENCY UNIT IN THE MODERN HOSPITAL. J. T. HOWELL AND R. C. BUERKI. Hospitals 31:37, March 16, 1957.

The emergency room that functions as a temporary medical haven for free service is rapidly disappearing and in its stead is appearing an emergency unit designed for total medical care. In the wake of scientific progress in medicine has come strong public interest in total medical care. The hospital has become the center of medical activity in the community, and its emergency unit has become an essential public service. The emergency unit must, therefore, be able to provide exacting and complete diagnosis and therapy at all hours of the day and night. Often the reputation of the entire hospital depends upon the quality and the speed of the medical care rendered in its emergency unit. Because of the multiple types of medical problems and the various professional relationships with the public, the emergency unit provides an excellent training opportunity for the resident and intern.

A LONG-TERM EVALUATION OF THE JUVENILE DIABETIC. T. JOOS AND J. A. JOHNSTON. J. Pediat. 50:133, 1957.

Of 150 juvenile diabetics, 44 whose disease had existed more than ten years, were selected for special study. All had been on a fixed dietary prescription, deriving calories 15 percent from protein, 50 percent from fat, and 35 percent from carbohydrate. Of these 59 percent had some vascular complication, though this did not appear until the disease had existed for over eleven years. There was a significant correlation between the incidence of complications and the adequacy of control of the diabetes. One patient has died of tuberculosis and three of Kimmelstiel-Wilson's disease. The caloric and insulin requirements of this group are plotted graphically to maturity. The sharp rise preceding, and the fall following, puberty are emphasized.

THE MEDICAL SOCIAL WORKER'S CONTRIBUTION. PAULINE M. RYMAN. *IN* EVALUATION OF REHABILITATION TO THE INDIVIDUAL — A PANEL DISCUSSION. Am. J. Orthopsychiat. 27:28, 1957.

Rehabilitation is a helping process through which a physically or emotionally handicapped individual is enabled to achieve satisfaction and usefulness to himself, his family and his community. The attainment of these goals may require employment of the knowledges and skills of multiple professional disciplines working together and use

of appropriate resources within the community. Prevention of extension of disability and promotion of achievement of self care should also be considered as appropriate goals of the rehabilitation team. The medical social worker contributes skill to the evaluation of the patient through knowledge of his social situation, family relationships, personality, previous work history, educational background and particularly of the meaning of the illness and disability to each patient. Through contacts with the patient and his family during the course of illness, workers are enabled to utilize to the fullest possible extent the opportunities for medical treatment. Through knowledge of the needs of the family and the impact of the illness situation on them, appropriate community resources may be employed in an effort to minimize social dislocation. When the medical treatment has achieved its maximum goal in respect to physical improvement the patient is helped to utilize appropriate resources to reach and maintain a suitable vocational goal in respect to his handicap. The use of the social worker's interpretation of the problems of the patient and his family may modify the attitudes of other members of the treatment team toward the patient on the basis of their increased understanding. Follow up studies by multi-discipline groups are needed in order to evaluate the longtime results of rehabilitation.

A SIMPLIFIED ENTROPION OPERATION: USE OF A HORIZONTAL PERMANENTLY BURIED SUTURE TIGHTENING THE ORBICULARIS. R. A. SCHIMEK. Am. J. Ophthal. 43:245, 1957.

Senile spastic entropion of the lower lid can be easily and quickly corrected by a new operative technique. A tiny skin incision is made 3 mm. below the lash border and another skin incision is made temporal to the outer canthus. A silk suture, which is to remain permanently buried, is (1) tied about orbicularis fibers in the nasal lid incision, (2) passed subcutaneously across the lid, and (3) pulled taut and tied about orbicularis fibers and fascia in the temporal incision. The skin incisions are closed with interrupted sutures. By contrast with older temporary suture methods, this operation uses a permanent buried horizontal suture to tighten the orbicularis over the lower portion of the tarsus which everts the upper border of the tarsus. This method is especially useful in previously operated entropion cases with secondary scar tissue, since it avoids difficult dissection and excessive bleeding. Excellent results were obtained in an operative series of 23 cases.

ABLATION THERAPY IN THE MANAGEMENT OF MENIERE'S DISEASE. H. F. SCHUKNECHT. Acta Oto-Laryngologica Supp. 132, 1957.

The article is a detailed description of the management of Ménière's disease. The vertigo and vomiting associated with Ménière's disease can become so severe and so frequent as to be incapacitating. At this stage the patient is fearful of having attacks while at work or on the street, and when so afflicted is willing to make some sacrifice to obtain relief of symptoms. A rational therapeutic approach to incapacitating unilateral Ménière's disease is surgical or medical ablation of the diseased inner ear. An effective surgical procedure is labyrinthotomy which may be accomplished through either a transmastoid or a trans-tympanic approach, the latter being preferred because of its simplicity. The medical method consists of injecting streptomycin sulfate solution into the middle ear through tubing of small caliber. This results in an equally effective

ablation of vestibular function in the treated ear. For incapacitating bilateral Ménière's disease the most effective treatment is the parenteral administration of streptomycin sulfate in amounts adequate to effect a nearly complete ablation of vestibular function.

CHANGES IN THE ACTIVITY OF TRANSAMINASES AND L-GLUTAMIC ACID DEHYDROGENASE INDUCED BY GROWTH HORMONE. A. C. Zuchlewski and O. H. Gaebler. Arch. Biochem. & Biophys. 66:463, 1957.

Changes in activity of L-glutamic acid dehydrogenase (GAD) and glutamic-pyruvic transaminase (G1-Py) in liver, and of glutamic-oxalacetic transaminase (Gl-Ox) in liver and muscle, were studied in groups of hypophysectomized rats injected with saline or growth hormone for 0,2,5, or 10 days, and in corresponding groups of sham-operated rats. Hepatic GAD activity was slightly but significantly higher in hypophysectomized rats than in sham-operated ones, and was not altered by growth hormone in either group. In sham-operated rats, hepatic G1-Py activity was unaffected by growth hormone in the dose employed (100 ug./day); in hypophysectomized rats, activity of this enzyme was progressively reduced in the groups treated with growth hormone for 2,5, and 10 days, only a fourth of the initial activity remaining in the last group. In muscle, progressive reduction of G1-Ox activity from the high level in hypophysectomized rats to a normal level, previously reported by Bartlett and Glynn, was confirmed. In liver, the changes in G1-Ox activity were more complicated. Incorporation of N^{15} from labeled alanine into plasma fibrinogen; into proteins of liver, spleen, kidney, and heart; and into collagen from Achilles tendon or tail, was only slightly greater in hypophysectomized rats treated with growth hormone than in untreated ones. Incorporation of N^{15} into collagen was less than one-fifth as great as incorporation into fibrinogen. Transfer of N^{15} from labeled alanine to glutamic acid, tyrosine, and other amino acids was similar in untreated hypophysectomized rats and in those treated with growth hormone in doses (100 ug./day) sufficient to produce nearly maximal gain in weight.